2025

MOH/P/PAK/595.25(GU)-E

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF MYELOPROLIFERATIVE NEOPLASMS

(SECOND EDITION)

Ministry of Health Malaysia

Malaysian Society of Haematology

Academy of Medicine of Malaysia

Developed and published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre
62590 Putrajaya, Malaysia

eISBN: 978-629-7842-19-6

Available on the following websites:
https://www.moh.gov.my
https://mymahtas.moh.gov.my
https://www.acadmed.org.my
https://haematology.org.my/

STATEMENT OF INTENT

This clinical practice guidelines (CPG) is meant to be a guide for clinical practice based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decision appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2025 and will be reviewed in a minimum period of four years (2029) or sooner if there is a need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

TABLE OF CONTENTS

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG DG as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

RISK STRATIFICATION CRITERIA

- Risk stratification should be performed upon diagnosis of myeloproliferative neoplasms subtypes prior to initiation of treatment.

NON-PHARMACOLOGICAL TREATMENT

- Phlebotomy should be considered in patients with polycythaemia vera.
- Splenectomy or splenic irradiation may be offered in myelofibrosis patients who are candidates for allogenic haematopoeitic stem cell transplant with palpable spleen >5 cm after suboptimal response with Janus kinase inhibitor treatment.

PHARMACOLOGICAL TREATMENT

- Aspirin should be given to all essential thrombocythaemia (ET) and polycythaemia vera (PV) patients including those stratified as low-risk unless contraindicated.
- Hydroxyurea should be used as the first-line agent for:
  - high-risk PV
  - intermediate- and high-risk ET
- Pegylated interferon may be considered in the treatment of high-risk ET and PV as an alternative for those who are intolerant or resistant to hydroxyurea.
- Ruxolitinib:
  - should be considered in treating intermediate- and high-risk myelofibrosis
  - may be considered as alternative for hydroxyurea-intolerant PV
- Allogeneic haematopoietic stem cell transplant may be considered for intermediate and high-risk myelofibrosis patients.
- Achieving spleen volume reduction either by pharmacological or non-pharmacological method should be aimed for a favourable transplant outcome.

TREATMENT FOR PREGNANT WOMEN

- A multidisciplinary approach should be implemented throughout antenatal care of women with myeloproliferative neoplasms (MPN).
- All women with MPNs should be given pre-pregnancy counselling prior to conception.
- All pregnant women with MPNs should be prescribed with aspirin unless contraindicated; its combination with low molecular weight heparin and/or interferon is preferred in high-risk patients.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the DG for this CPG were from the Ministry of Health (MoH) and private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and others e.g. PubMed (refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all adults with common *BCR::ABL1* negative myeloproliferative neoplasms (MPNs) regardless of study design. The first search was limited to literature published in the last 20 years (2004 until 2023) for all clinical questions, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed. All searches were conducted from 27 until 30 October 2023. The literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 11 February 2025 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines on MPN as listed below:

- World Health Organization (WHO) Classification of Tumours Editorial Board - Haematolymphoid Tumours 5th edition (2022)
- British Society for Haematology (BSH) - A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline (2019)
- European Leukemia Net (ELN) - Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet (2019)
- European Society for Medical Oncology (ESMO) - Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2015)
- Korean Association of Internal Medicine - The 2020 revision of the guidelines for the management of myeloproliferative neoplasms (2021)
- National Comprehensive Cancer Network (NCCN) - Myeloproliferative Neoplasms, Version 2.2024 (2024)

A total of 11 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG

members met 21 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using the Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews/meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the U. S. Preventive Services Task Force Level of Evidence (2015) while the grading of recommendation was done using the principles of GRADE as much as possible (refer to the preceding page). The writing of the CPG followed strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Upon completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from the **Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015** (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of MPN on the following aspects:

- diagnosis and investigation
- treatment (including risk stratification)
- follow-up and referral

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- All adults with common *BCR::ABL1* negative MPN
  - Polycythaemia vera (PV)
  - Essential thrombocythaemia (ET)
  - Primary myelofibrosis (PMF)
  - Post-PV myelofibrosis (MF)
  - Post-ET MF

Exclusion Criteria

- Chronic myeloid leukaemia
- Other MPN subtypes
  - Chronic neutrophilic leukaemia
  - Chronic eosinophilic leukaemia
  - MPN, not otherwise specified

TARGET GROUP/USER

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care of both public and private sector in the management of MPN including:

i. medical doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients, caregivers and their advocates
v. professional societies
vi. policy makers

HEALTHCARE SETTINGS

Primary, secondary and tertiary care

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *United States (U.S.) Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG DG.
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

DEVELOPMENT GROUP

Chairperson
Dr. Lau Ngee Siang
Consultant Clinical Haematologist
Hospital Ampang, Selangor

Members (in alphabetical order)

Dr. Ahlam Naila Kori
Consultant Clinical Haematologist
Hospital Tengku Ampuan Afzan, Pahang

Associate Professor Dr. Asral Wirda Ahmad Asnawi
Consultant Haematopathologist
Sunway Medical Centre, Selangor

Dr. Dang Chee Chean
Pharmacist
Hospital Melaka, Melaka

Dr. Gan Chye Lee
Consultant Physician &
Acute Internal Medicine
Hospital Melaka, Melaka

Dr. Johan Siow Way Han
Head of Department & General Physician
Hospital Segamat, Johor

Dr. Karen Sharmini Sandanasamy
Head of CPG Unit &
Public Health Physician
Malaysian Health Technology Assessment Section, Ministry of Health, Putrajaya

Dr. Lim Ee Shuan
General Surgeon
Hospital Ampang, Selangor

Dr. Mohamad Zikri Mohamad Isa
Family Medicine Specialist
Klinik Kesihatan Lintang, Perak

Dr. Mohd Aminuddin Mohd Yusof
Public Health Physician

Dr. Siti Nuryati Che Ya
Family Medicine Specialist
Klinik Kesihatan Pulai Chondong, Kelantan

Dr. Siti Shahrum Muhamed Said
Consultant Haematopathologist
Hospital Tunku Azizah, Kuala Lumpur

Dr. Tengku Noor Farhana Tengku Khalid
Public Health Physician
Malaysian Health Technology Assessment Section, Ministry of Health, Putrajaya

Dr. Veena V Selvaratnam
Consultant Haematologist
Hospital Ampang, Selangor

Dr. Wong Shu Ping
Pharmacist
Hospital Ampang, Selangor

REVIEW COMMITTEE

The draft CPG was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the CPG.

Chairperson

Dr. Lily Wong Lee Lee
Senior Consultant Haematologist
Hospital Queen Elizabeth I, Sabah

Members (in alphabetical order)

Mr. Azidi Ameran
Patient Advocate

Professor Dr. Gan Shiaw Sze @ Gan Gin Gin
Senior Consultant Haematologist
Universiti Malaya, Kuala Lumpur

Ms. Goh Jiet Hui
Pharmacist
Hospital Sultanah Aminah, Johor

Dr. Izzuna Mudla Mohamed Ghazali
Deputy Director & Public Health Physician
Malaysian Health Technology Assessment Section, Ministry of Health, Putrajaya

Ms. Lee Pooi Mun
Pharmacist
Hospital Raja Permaisuri Bainun, Perak

Professor Dr. Raja Zahratul Azma Raja Sabudin
Senior Consultant Haematopathologist
Universiti Kebangsaan Malaysia
Kuala Lumpur

Dr. Raudhawati Hj Osman
Senior Consultant Haematopathologist
Hospital Melaka, Melaka

Dr. Teoh See Wie
Family Medicine Specialist
Klinik Kesihatan Salak, Selangor

Dr. Yoon Chee Kin
Senior Consultant Acute Internal Medicine
Hospital Pulau Pinang, Pulau Pinang

EXTERNAL REVIEWERS (alphabetical order)

The following external reviewers provided feedback on the draft:

Dr. Aznita Ibrahim
Head of Department &
Consultant Internal Medicine
Hospital Sultan Abdul Halim, Kedah

Dr. Goh Choon Seong
Family Medicine Specialist
Klinik Pakar Perubatan Kuala Kangsar,
Perak

Mr. Ko Ching Tiong
Pharmacist
Hospital Umum Sarawak, Sarawak

Professor Dr. Ng Soo Chin
Senior Consultant Haematologist
Subang Jaya Medical Centre,
Selangor

Dr. Nor Huda Mat Ali
Consultant Gynaeoncology &
Consultant Obstetrics & Gynaecology
Hospital Tengku Ampuan Afzan,
Pahang

Dr. Nur Amirah Shibraumalisi
Lecturer & Family Medicine Specialist
Universiti Teknologi MARA, Selangor

Dr. Nur Dalila Noor Azman Shah
Head of Department &
Internal Medicine Physician
Hospital Bintulu, Sarawak

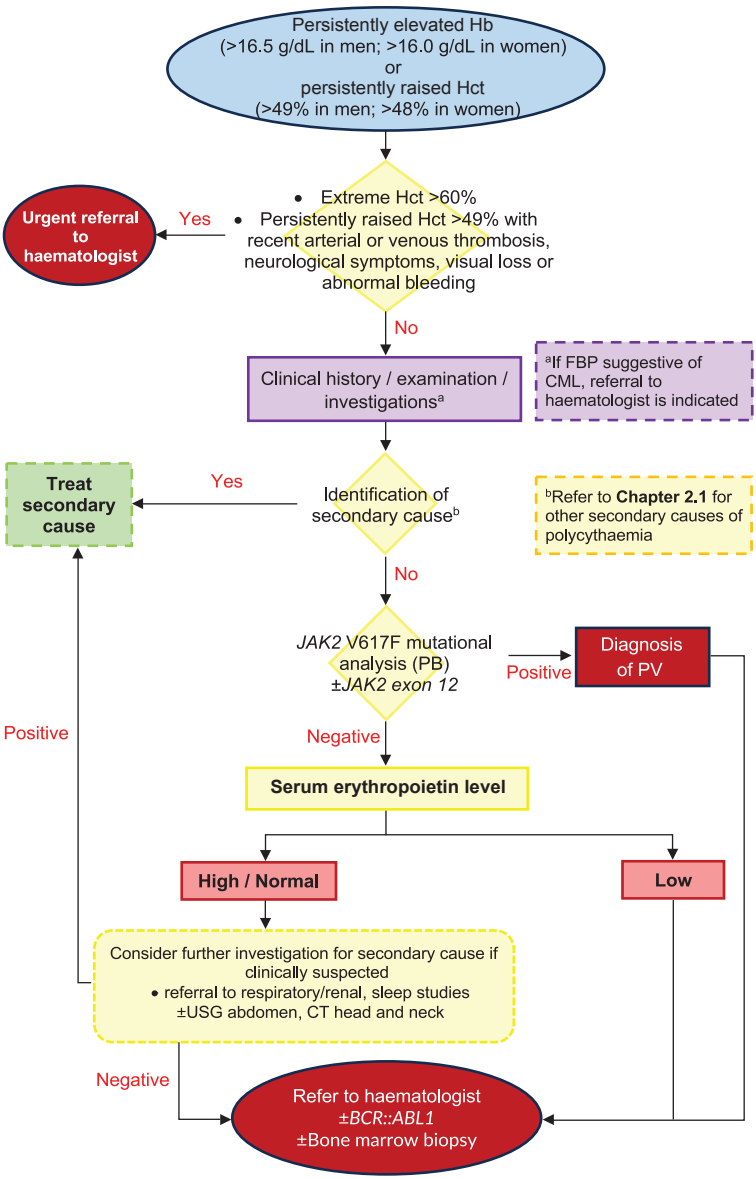
Professor Dr. Rosline Hassan
Senior Consultant Haematologist
Universiti Sains Malaysia, Kelantan

Dr. V Paranthaman P Vengadasalam
Consultant Family Medicine Specialist
Klinik Kesihatan Mahmoodiah, Johor

Dr. Yuslina Mat Yusoff
Haematopathologist
Institute of Medical Research
Institut Kesihatan Negara, Selangor

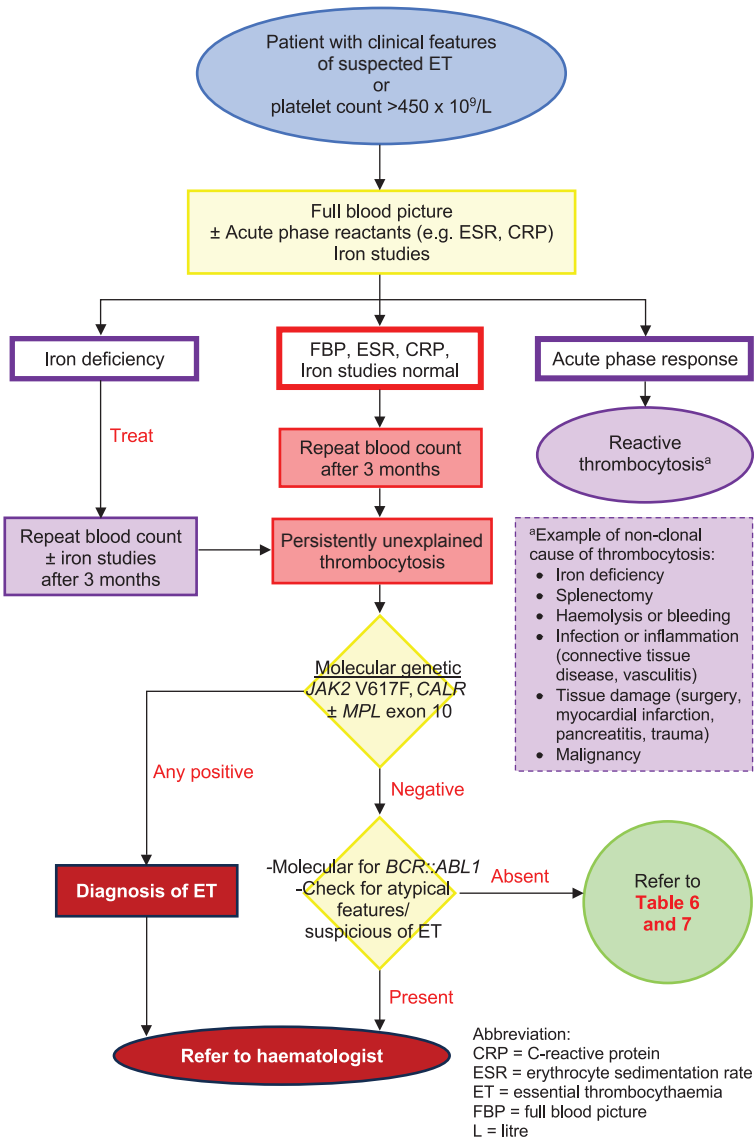
Dr. Yang Khuan Fuat
Consultant Hepatobiliary & General Surgery
Hospital Pantai Ayer Keroh, Melaka

ALGORITHM 1: DIAGNOSTIC ALGORITHM FOR POLYCYTHAEMIA

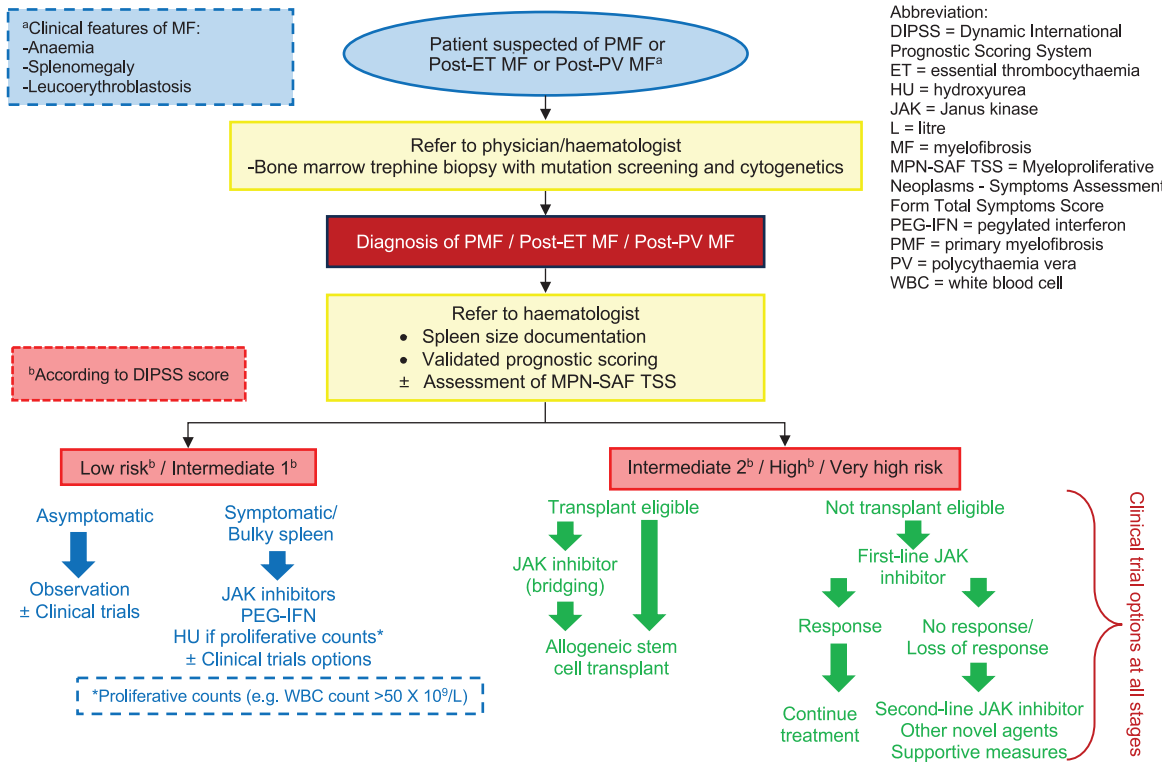


Abbreviation:
CML = chronic myeloid leukaemia; CT = computed tomography; g/dL = gram per decilitre; FBP = full blood picture; Hb = haemoglobin; Hct = haematocrit; PB = peripheral blood; PV = polycythaemia vera; USG = ultrasonography

ALGORITHM 2: DIAGNOSTIC ALGORITHM FOR THROMBOCYTOSIS

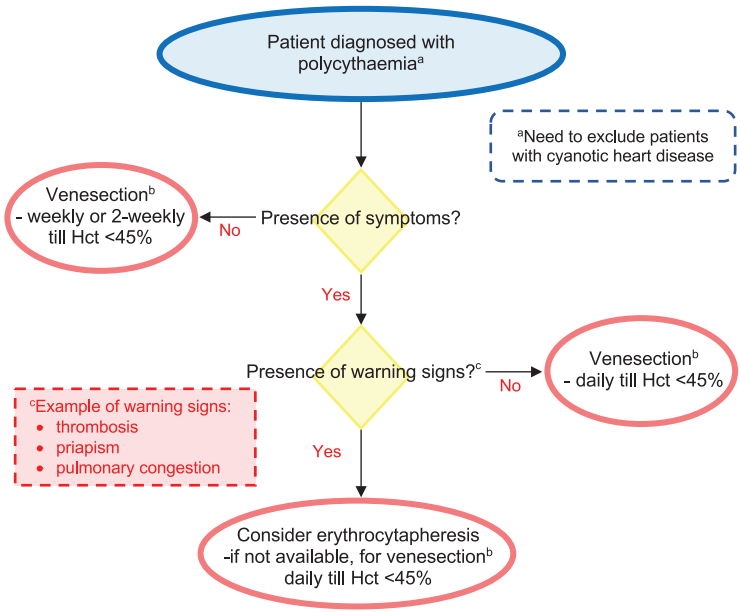


ALGORITHM 3: MANAGEMENT OF MYELOFIBROSIS



Abbreviation:
DIPSS = Dynamic International Prognostic Scoring System
ET = essential thrombocythaemia
HU = hydroxyurea
JAK = Janus kinase
L = litre
MF = myelofibrosis
MPN-SAF TSS = Myeloproliferative Neoplasms - Symptoms Assessment Form Total Symptoms Score
PEG-IFN = pegylated interferon
PMF = primary myelofibrosis
PV = polycythaemia vera
WBC = white blood cell

ALGORITHM 4: POLYCYTHAEMIA VENESECTION



KEY POINTS:

- All patients should be on aspirin, caution for patients with acquired von Willebrand syndrome
- [b]Target of venesection: Hct of 45% (equates to Hb of 15 g/dL) in PV
- [b]Blood should be venesected over ≥15 minutes to a maximum of 7 mL/kg, i.e. ≈ 400 mL in <60 kg, ≈ 500 mL in 70 kg, ≈ 650mL in 90 kg using likely lean body weight.
- Isovolaemic dilution (500 mL of 0.9% sodium chloride either concurrently or immediately after venesection) may be preferable if the aim is to produce rapid reduction of Hb
- Equilibration after venesection takes 36 - 48 hours and in PV patients with a markedly raised total blood volume, there may be little reduction in Hct until several venesections have been performed

Abbreviation:
g/dL = gram per decilitre; Hb = haemoglobin; Hct = haematocrit; i.e. = that is; kg = kilogram; mL = millilitre; mL/kg = millilitre per kilogram; PV = polycythaemia vera

1. INTRODUCTION

Myeloproliferative neoplasms (MPN) are a group of haematologic disorders characterised by clonal expansion of haematopoietic stem cells leading to increased production of one or more blood cells lineages.

MPNs are divided into two major subclasses namely *BCR::ABL1*-positive chronic myeloid leukaemia (CML) and *BCR::ABL1*-negative MPNs. The latter includes essential thrombocythaemia (ET), polycythaemia vera (PV), and primary myelofibrosis (PMF)[1] which will be discussed further in detail in the current CPG.

MPNs are all closely related and have an intrinsic tendency to evolve into acute myeloid leukaemia (AML), confirming their classification as haemato-oncological disorders. They are characterised by an increased incidence of thrombosis about 20 - 30% over 15 years and premature death for the majority of patients.[2, level III]

The Surveillance, Epidemiology and End Results (SEER) Program estimates worldwide incidence rates of 1.09 per 100,000 for PV, 0.96 per 100,000 for ET and 0.31 per 100,000 for PMF.[3, level II-2] Prevalence of MPN across different countries remains difficult to determine due to the differences in reporting methods.

A total of 1,010 MPN patients were registered in 11 centres across Malaysia between 2009 to 2015. The mean age was 54 years with male predominance. The ethnic distribution revealed that Chinese had a relatively high weighted incidence proportion (43.2%), followed by Indian (23.8%), Malay (15.8%) and other ethnic groups (17.2%). The types of MPN reported were 40.4% of ET, 38.1% of PV, 9.2% of PMF, 3.1% of hypereosinophilic syndrome (HES) and 7.9% of unclassifiable MPN (MPN-U).[4, level III]

Since the publication of the CPG on the Diagnosis and Management of Myeloproliferative Disorders in 2004, the World Health Organization (WHO) classification of myeloid neoplasms has been revised till the 5th edition in 2022 to incorporate new clinical, morphologic and genetic data and prognostication values into MPNs diagnosis. There are also many new laboratory developments since the discovery of Janus kinase/signal transducers and activators of transcription (JAK-STAT) “driver” mutations (e.g. *JAK2*). These aid the diagnosis of MPNs in line with conventional bone marrow morphologic evaluation findings.

The development and availability of targeted therapies (e.g. *JAK2* inhibitors) have improved disease-related symptoms and quality of life (QoL) particularly in PMF patients. However, challenges remain for

clinical haematologists to harness available therapeutic approaches in improving the overall survival of MPN patients.

With the above reasons, a timely revision of this CPG is important to assist physicians, clinical haematologists and other healthcare providers in improving the many aspects of clinical management concerning MPNs which include disease and symptom burden assessment, various treatment modalities and prevention of complications. It also features new chapters on MPNs with pregnancy, monitoring and referral.

2. DIAGNOSIS AND INVESTIGATION

Given the overlap in clinical presentations among MPN subtypes, accurate diagnosis of *BCR::ABL1*-negative MPN requires integrating clinical features with morphology, cytogenetic and molecular findings.

2.1. Clinical Features

Among the MPN disorders, Philadelphia chromosome-negative MPNs [which do not involve the Philadelphia chromosome (Ph)], represent a distinct subgroup with specific clinical features, pathophysiology and diagnostic criteria.

The main disease entities remain unchanged from the previous edition. These conditions can vary significantly in terms of clinical presentation, disease progression and associated complications, yet all share a tendency for excessive blood cell production and potential for transforming into AML and myelofibrosis (MF) over time. The clinical manifestations of these disorders are often subtle and non-specific early in the disease course, yet can lead to severe thrombotic vascular events as they progress.

Example of thrombotic events are:

- cerebrovascular accident
- transient ischaemic attack
- retinal artery or venous occlusion
- myocardial infarction (MI)
- pulmonary embolism (PE)
- hepatic or portal vein thrombosis
- deep vein thrombosis (DVT)
- peripheral vascular disease

Thrombosis at unusual sites (e.g. hepatic, portal and mesenteric veins) is frequently associated with an underlying MPN. However, local or systemic inflammatory conditions need to be excluded as potential causes. Approximately 40% of patients with underlying MPN suffer recurrent thrombosis.[5, level III]

- Routine screening of MPN is indicated in patients presenting with thrombosis at unusual sites.

Understanding the clinical features of *BCR::ABL1*-negative MPNs is critical for accurate diagnosis and appropriate management. This includes recognising the common symptoms, laboratory findings and potential complications that help differentiate these conditions from other haematological or systemic diseases.

2.1.1. Polycythaemia vera

a. Clinical features

Most PV patients are asymptomatic and only discover the disease during routine blood tests. There are some common symptoms in relation to PV e.g. microvascular symptoms and thrombotic events.

The major symptoms are related to hyperviscosity caused by the increased red cell mass. Microvascular symptoms would include headaches, light-headedness, blurred vision, paraesthesia, plethora, erythromelalgia and aquagenic pruritus. Episodes of severe erythema and burning pain in reaction to heat stimuli are known as erythromelalgia. Generalised pruritus that occurs after being in water, usually while taking a hot bath, is known as aquagenic pruritus.[1; 6] Other findings may include arthritic pain and rarely haemorrhage, particularly from the gastrointestinal tract.

In nearly 25% of patients, an episode of venous or arterial thrombosis, i.e. deep vein thrombosis (DVT), MI or stroke, is the first manifestation. Mesenteric, portal or splenic vein thrombosis should always lead to the differential of PV.

Physical findings include phlethora in 70% of patients, palpable splenomegaly in 70% and hepatomegaly in 40%.[6] Laboratory findings at presentation show erythrocytosis and may include leucocytosis and/or thrombocytosis. An iron deficiency state may also be present.

However, secondary causes of polycythaemia need to be excluded before the diagnosis of PV. The list of secondary causes of polycythaemia is as follows:[6]

i) Relative (reduced plasma volume)
   - Dehydration

ii) Absolute (increase in red cell mass)
   - Primary (acquired or germline/inherited mutations)
     - Acquired:
       - Polycythaemia vera
       - Other myeloproliferative disorders
     - Inherited:
       - High affinity haemoglobinopathies
       - Erythropoietin (EPO) receptor mutations
   - Secondary (caused by elevated serum EPO)
     - Appropriate physiological response to tissue hypoxia:
       - Alcohol excess
       - Chronic lung diseases
       - Obstructive sleep apnoea/Obesity
       - Cyanotic heart disease
       - Right to left cardiac shunt
       - High altitude

- Renal disease (e.g. hydronephrosis, renal cysts, renal artery stenosis)
- Inappropriate EPO production:
  - EPO-producing tumours (e.g. renal cell carcinoma, hepatocellular carcinoma, cerebellar haemangioblastoma, meningioma and parathyroid carcinoma/adenoma)
- Drug induced [e.g. testosterone, growth hormone, EPO, diuretics and sodium-glucose co-transporter 2 (SGLT2) inhibitor]

b. Prognosis

Risk factors for leukaemic transformation include age and leukocytosis which occurs in 5.5 - 18.7% of patients within 15 years.[7, level III; 8, level II-2]

As defined in a retrospective cohort study, both low-risk ET [International Prognostic Score for Thrombosis in Essential Thrombocythaemia (IPSET) score of 0] and low-risk PV [age <57 years old, white blood count (WBC) <15 x 10^9/L and absence of venous thrombosis] displayed excess mortality relative to age- and sex-matched controls with median survival of 26.7 and 28.1 years, respectively, compared to the expected 37.5 and 39.2 years ($p<0.001$).[9, level II-2]

2.1.2. Essential Thrombocythaemia

a. Clinical features

Patients with ET usually present with asymptomatic thrombocytosis that is detected by standard testing. Symptoms of ET are similar with the microvascular features of PV. Thrombotic events may occur at a wide range of platelet counts.

Bleeding events can complicate ET and clinician must look for an un-diagnosed acquired von Willebrand syndrome. Patients with extreme thrombocytosis (>1,000 x 10^9/L) without haemorrhagic events may also warrant investigation for acquired von Willebrand syndrome before the initiation of antithrombotic therapy.

Less common features include night sweats, pruritus, mild splenomegaly and splenomegaly-related symptoms.[1]

b. Prognosis

ET is an indolent disease that may be interspersed with sporadic potentially fatal thromboembolic or haemorrhagic episodes,[10, level II-2] with 10 - 15% of patients progressing to post-ET myelofibrosis (MF) after many years.[11, level II-2]

A multicentre cohort study using 2008 WHO criteria in the diagnosis of ET and early/prefibrotic PMF showed:[12, level II-2]

- early/prefibrotic PMF increased risk of death (HR=1.6, 95% CI 1.05 to 2.44), leukaemia transformation (HR=4.5, 95% CI 1.52 to 13.3) and progression to MF (HR=2.35, 95% CI 1.15 to 4.8)
- ET had significantly better overall survival (OS), leukaemia-free survival and overt MF-free survival
- irrespective of diagnosis, death was significantly higher in those aged >60 years, WBC count >11 x 10^9/L, haemoglobin (Hb) level <12 g/dL and previous thrombosis

2.1.3. Primary Myelofibrosis

a. Clinical features

PMF is a presentation of MF that does not have a prior diagnosis of PV or ET, as opposed to secondary MF, which is characterised by a transformation of disease. About 20% of patients are asymptomatic and detected incidentally due to the presence of splenomegaly or from routine blood smear findings of leucoerythroblastic features or cytopenia.[6]

The majority may present with:[6]

- hypercatabolic symptoms
  - severe fatigue
  - low grade fever
  - night sweats
  - weight loss
- extramedullary haemopoeisis caused by marrow fibrosis
  - hepatomegaly
  - painful splenomegaly
  - lymphadenopathy
  - ascites
  - pleural effusion
  - cord compression secondary to paraspinal and epidural masses
- portal hypertension
- bone pains

b. Prognosis

i) Pre-fibrotic or early stage

Pre-PMF is a subtype of PMF characterised by a hypercellular bone marrow, minimal to absent reticulin fibrosis (grade 0 or 1) and a more latent disease course compared with fibrotic PMF.[1]

ii) Fibrotic PMF

Fibrotic PMF indicates progression to the accelerated phase and may be followed by transformation to acute leukaemia. Low-risk patients may expect a median survival of eight to 10 years whereas the high-risk group may survive <3 years.[6]

In another multicentre retrospective cohort study on patients with PMF based on the revised 2016 WHO criteria for diagnosis of PMF, the findings were:[13, level II-2]

- in patients with lower International Prognostic Scoring System (IPSS) risk, fibrosis grade ≥2 was associated with shorter survival compared with grade 1 (15.4 years vs 22.8 years, HR=1.9, 95% 1.1 to 3.2)
- in younger patients, fibrosis grade 2 and 3 significantly reduced median survival compared with grade 1 (6.7 years, 7.2 years and 14.7 years, respectively)
- high molecular risk (HMR) mutant gene (referred to the presence of somatic mutation in *ASXL1, EZH2, IDH1, IDH2* and *SRSF2*) and those harbouring ≥2 HMR or had unfavourable karyotypes were significantly associated with fibrosis grade ≥2

2.2. Investigations

A cross-sectional analysis of patients with PV and ET showed considerable limitations of discriminating these two subtypes solely based on red cell parameters.[14, level III]

WHO guidelines on diagnosis of MPN has been updated in 2022 and address on the importance of morphological and genomic findings as discussed below based on subtypes of MPN.[1]

a. Diagnostic criteria

i) Polycythaemia vera

Diagnosis of PV requires either **all three major criteria** or **first two major criteria and minor criterion**.
Major Criteria: 1. Elevated Hb concentration (>16.5 g/dL in men; >16.0 g/dL in women) or elevated haematocrit (Hct) (>49% in men[a], >48% in women) 2. Bone marrow (BM) showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes differences in size *(BM biopsy may not be required in patients with sustained absolute erythrocytosis (Hb concentrations of >18.5 g/dL in men and >16.5 g/dL in women or Hct values of >55.5% in men and >49.5% in women) if major criterion '3' and the minor criterion are present.)* 3. Presence of *JAK2* V617F or *JAK2* exon 12 mutation
Minor Criteria: ○ Subnormal serum EPO level

[a]Hct for diagnosis in the presence of a *JAK2* mutation. In the absence of *JAK2* mutation, a higher Hct target (e.g. 52%) could be considered in men before further investigation is required.

ii) Essential thrombocythaemia

Diagnosis of ET requires either **all major criteria** or **first three major criteria and a minor criterion** to be met.

Major criteria:

1. Platelet count ≥450 ×10^9/L
2. BM biopsy showing proliferation mainly of megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; very rarely a minor (grade 1) increase in reticulin fibres[a]
3. WHO criteria for *BCR::ABL1*-positive CML, PV, PMF and other myeloid neoplasms are not met
4. *JAK2, CALR* or *MPL* mutation

Minor criteria:

- Presence of a clonal marker[b] OR exclusion of reactive thrombocytosis

[a]In local healthcare setting, BM biopsy may not be performed if *JAK2, CALR* or MPL mutation is positive and prefibrotic PMF is not clinically suspected.
[b]Examples of clonal markers are *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2* and *SF3B1* mutations.

iii) Primary myelofibrosis, prefibrotic

Diagnosis of prefibrotic PMF requires **all three major criteria and at least one minor criterion** to be confirmed in two consecutive determinations.

Major criteria:

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation and (often) decreased erythropoiesis
2. Not meeting diagnostic criteria for CML, PV, ET, myelodysplastic neoplasms or other defined myeloid neoplasms
3. *JAK2, CALR* or *MPL* mutation or presence of another clonal markera or absence of reactive BM fibrosis[b]

Minor criteria:

1. Anaemia not attributed to a co-morbid condition
2. Leucocytosis ≥11 x 10^9/L
3. Splenomegaly detected clinically and/or by imaging
4. Lactate dehydrogenase (LDH) level above upper limit of institutional reference range

[a]In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g. *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2* and *SF3B1* mutations) may be helpful in determining the clonal nature of the disease.

[b]Minor reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukaemia or another lymphoid neoplasm, metastatic malignancy or toxic (chronic) myelopathies.

iv) Primary myelofibrosis, fibrotic stage

Diagnosis of overt PMF requires **all three major criteria and at least one minor criterion** to be met in two consecutive determinations.
Major criteria: 1. Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grade 2 or 3 2. Not meeting diagnostic criteria for CML, PV, ET, myelodysplastic neoplasms or other defined myeloid neoplasms[a] 3. *JAK2, CALR* or *MPL* mutation or presence of another clonal marker[b] or absence of reactive BM fibrosis[c]
Minor criteria: 1. Anaemia not attributed to a co-morbid condition 2. Leucocytosis ≥11 x 10^9/L 3. Palpable splenomegaly 4. LDH level above the reference range 5. Leucoerythroblastosis

[a]MPNs can be associated with monocytosis or patients can develop it during the course of the disease. These cases may mimic chronic myelomonocytic leukaemia (CMML); in these rare instances, a history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or MPN-associated mutations (in *JAK2, CALR* or *MPL*) tends to support the diagnosis of MPN with monocytosis rather than CMML.
[b]In the absence of any of three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g. *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2* and *SF3B1* mutations) may be helpful in determining clonal nature of the disease.
[c]BM fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukaemia or another lymphoid neoplasm, metastatic malignancy or toxic (chronic) myelopathies.

v) Post-polychythaemia vera myelofibrosis

Diagnosis of post-PV MF requires **all required criteria and at least two additional criteria**.
Required criteria: 1. Documentation of a previous diagnosis of WHO-defined PV 2. BM fibrosis of grade 2 - 3 on a scale of 0 - 3
Additional criteria (two are required): 1. Anaemia (below reference range, given age, sex and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. Leucoerythroblastosis

3. Increasing splenomegaly, defined as either an increase in palpable splenomegaly of >50 mm from baseline (distance from left costal margin) or development of a newly palpable splenomegaly
4. Development of any two (or all three) of the following constitutional symptoms: >10% weight loss in six months, night sweats, unexplained fever (>37.5°C)

vi) Post-essential thrombocythaemia myelofibrosis

Diagnosis of post-ET MF requires **all required criteria and at least two additional criteria**.

Required criteria:
1. Documentation of a previous diagnosis of WHO-defined ET
2. BM fibrosis of grade 2 - 3 on a scale of 0 - 3

Additional criteria:
1. Anaemia (below reference range, given age, sex and altitude considerations) and a >2 g/dL decrease from baseline Hb concentration
2. Leucoerythroblastosis
3. Increasing splenomegaly, defined as either an increase in palpable splenomegaly of >50 mm from baseline (distance from left costal margin or on imaging) or development of newly palpable splenomegaly
4. Elevated LDH level (above reference range)
5. Development of any two (or all three) of the following constitutional symptoms: >10% weight loss in six months, night sweats, unexplained fever (>37.5°C)

In a retrospective cohort study on MF progression in ET, the findings were:[15, level II-2]

- significant prognostic factors were male, splenomegaly, constitutional symptoms and mutational status (*CALR* type 1/1-like and *MPL*)
- higher transformation risk in HMR [*JAK2* V617F variant allele frequency (VAF) >35%, *CALR* type 1/1-like or *MPL*] than low molecular risk (*JAK2* V617F VAF ≤35%, *CALR* type 2/2-like or triple negative) with HR of 5.2 (95% CI 2.7 to 10)

b. Full blood count

The full blood count (FBC) is a simple yet essential investigation and represents the first step in the diagnostic evaluation of MPNs. Readily available in both primary care and hospital settings, it is crucial role not only in screening and initial detection, but also for monitoring treatment response and identifying disease relapse.

c. Morphology

The degree of fibrosis in BM trephine biopsy is important to differentiate the diagnosis of ET and prefibrotic PMF.

A previous multicentre cohort study using 2008 WHO criteria showed significantly higher frequency of grade 1 BM fibrosis, median of WBC count, median of platelet count, median of circulating blast cells, median of serum LDH level and incidence of palpable splenomegaly but lower median Hb level in early/prefibrotic PMF compared with ET.[12, level II-2]

In the same cohort study mentioned earlier on patients with PMF based on the revised 2016 WHO diagnostic criteria, presence of fibrosis grade 2 and 3 at diagnosis was significantly associated with more advanced disease [anaemia, leucopenia, thrombocytopenia, more frequent constitutional symptoms, larger splenomegaly, higher IPSS risk category and increasing number of peripheral blood (PB) blast].[13, level II-2]

- The WHO grading system for MF (grade 0 - 3) should be used consistently to describe the degree of fibrosis in MPN.[1]

d. Lactate dehydrogenase

The WHO classification for haematolymphoid diseases was recently updated in 2022.[1] Serum LDH level has been retained as an inclusion criterion for diagnosis of different stages of PMF and post-ET MF.

In a retrospective cohort study on PMF patients, the findings on serum LDH were:[16, level II-2]

- significantly higher level in overt PMF (mean of 532 U/L; range 136 - 2263) than pre-PMF (mean of 401 U/L; range 180 - 1237)
- level ≥1000 U/L was predictive of shorter survival (HR=1.7, 95% CI 1.1 to 2.6), along with age >65 years, Hb <10 g/dL, platelets <100 $\times 10^9$/L, leucocyte count >25 $\times 10^9$/L and presence of constitutional symptoms
- survival comparison stratified by different levels showed significantly shorter survival with serum LDH ≥1000 U/L (2.7 vs 4.6 years)
- marked elevation independently predicted shorter survival (HR=2.2, 95% CI 1.3 to 3.6); further analysis of genetic mutations showed absence of *CALR* type 1/like, presence of mutated *ASXL1* and unfavourable karyotype were significantly associated with shorter survival

In another retrospective cohort study of patients with ET, increased serum LDH level showed:[17, level II-2]

- association with leucocytosis ≥11 x10^9/L, thrombocytosis, palpable splenomegaly and higher IPSET risk

- NS association with age, gender, Hb, leucoerythroblastosis, driver mutational status *TET2/ASXL1* mutations or thrombosis history
- significant lower survival in patients with leucocytosis

A comparison of three major classification systems using LDH in the diagnosis of PMF [The Italian Cooperative Study Group (ICSG), Campbell and Green (C&G) and WHO 2008] showed that the overall concordance among them was close to 80%.[18, level III]

e. Serum erythropoietin

Accurate diagnosis of PV is crucial for appropriate management and differentiating it from other causes of erythrocytosis. One of the key diagnostic markers in distinguishing PV from secondary causes of polycythaemia is serum EPO levels. In PV, EPO levels are typically low due to autonomous erythropoiesis driven by the *JAK2* V617F mutation. In contrast, secondary polycythaemia has elevated EPO levels in response to hypoxia or other stimuli.

A diagnostic study assessing serum EPO level in patients with PV revealed:[19, level III]

- low level was associated with PV (OR=0.857, p<0.001) where nearly 70% of patients had levels below the lower limit of normal
- a lower-than-normal range of EPO did not bring additional diagnostic value when *JAK2* V617F mutation was positive

f. Molecular analysis

Molecular testing plays a crucial role in diagnosing MPN. While *JAK2, CALR,* and *MPL* driver mutations are found in over 95% of PV and 85 - 90% of ET and PMF patients, advanced Next-Generation Sequencing (NGS) platforms now allow for the detection of additional mutations in genes such as *ASXL1, EZH2, TET2, IDH1, IDH2,* and *SRSF2*. Although not exclusive to MPN, their presence offers significant diagnostic value, leading to their inclusion as major criteria in the in the WHO's 2022 diagnostic criteria for MPN.[1]

Two meta-analyses and two retrospective cohort studies had shown that the distribution of *JAK2, CALR* and *MPL* mutations in MPN were as follows:[20, level III; 21, level III; 22, level II-2; 23, level II-2]

Mutations	PV (%)	ET (%)	PMF (%)
JAK2	95.0	57.0 - 59.2	53.2 - 60.0
CALR	0.0	19.0 - 25.1	22.0 - 35.5
MPL	0.0	3.5	6.0 - 6.4
Wild-type	5.0	12.2	4.9 - 12.0

**JAK2, CALR* and *MPL* mutations were mutually exclusive in ET and PMF patients

In a meta-analysis of 18 studies among patients with *BCR::ABL1*-negative MPNs:[24, level III]

- risk of *JAK2* mutations was higher in PV compared with ET and PMF patients [OR of 3.0 (95% CI 2.0 to 4.4) and 4.0 (95% CI 2.3 to 7.0), respectively]
- NS difference in the risk of *JAK2* mutations between ET and PMF patients
- risk of *MPL* mutations was lower in ET compared with PMF patients (OR=0.3, 95% CI 0.2 to 0.6)
- NS difference in the risk of *CALR* mutations between ET and PMF patients

No proper quality assessment of primary studies was addressed in this meta-analysis.

Two meta-analyses on patients with ET showed that presence of *JAK2* mutations:

- conferred an OR of 2.35 (95% CI 1.83 to 3.02) for thrombosis[20, level III]
- was associated with increased risk of thrombosis compared with wild-type *JAK2* (OR=1.92, 95% CI 1.45 to 2.53); subgroup analysis showed the odds for - [25, level II-2]
    - venous thrombosis was 2.49 (95% CI 1.71 to 3.61)
    - arterial thrombosis was 1.77 (95% CI 1.29 to 2.43)

However, there was no quality assessment done of the primary studies for both meta-analyses.

A retrospective cohort study on patients with Philadelphia chromosome-negative MPN showed that:[23, level II-2]

- when compared with *JAK2* mutation, those with *CALR* mutation had significantly -
    - lower Hb level, lower WBC count and higher platelet count at diagnosis among ET patients
    - lower WBC count and higher platelet count among PMF patients
- independent prognostic factors were as follows -
    - PMF was associated with shorter OS than ET (HR for death=7.1, 95% CI 4.9 to 10.2)
    - PMF patients with *CALR* mutation had significantly longer OS than *JAK2* V617F mutation or *MPL* mutation (median of 21.4 years, 11.0 years and 8.2 years, respectively); NS difference in OS between *JAK2* V617F and *MPL* mutations
    - ET patients with *CALR* mutation had significantly longer OS than *JAK2* V617F mutation
    - ET patients with *CALR* mutation had significantly lower risk of thrombosis than *JAK2* mutation

A retrospective cohort study on PMF patients showed:[22, level II-2]

- non-driver mutations [deoxyribonucleic acid (DNA) sequence variants/mutations other than *JAK2/CALR/MPL*] were detected

in 81% of overall patients; the most frequent variants/mutations detected were *ASXL1* (36%), *TET2* (18%), *SRSF2* (18%) and *U2AF1* (16%)

- prognostic relevance of the variants/mutations -
  - *ASXL1, SRSF2, CBL, KIT, RUNX1, CEBPA,* and *SH2B3* variants/mutations were identified as being adverse and at least one of them was present in 56% of the study patients -
    - *ASXL1, SRSF2, CBL,* and *KIT* were significantly associated with poorer survival (HR of 2.1, 2.0, 3.0 and 38.1, respectively)
    - *SRSF2, RUNX1, CEBPA* and *SH2B3* showed significant associations with leukaemia-free survival (HR of 4.9, 8.7, 5.4 and 5.8, respectively)
  - median survivals in patients with 0, 1 - 2 or ≥3 adverse variants/mutations were 8.5, 4 and 0.7 years, respectively ($p<0.001$); the difference was independent of Dynamic International Prognostic Scoring System (DIPSS)-Plus (DIPSS+) with HR of 7.3 (95% CI 3.2 to 16.8) for ≥3 and 1.9 (95% CI 1.2 to 3.0) for 1 - 2 adverse variants/mutations compared with 0

In a retrospective cohort study, the following parameters were helpful in predicting *JAK2* positivity among patients with PV:[26, level III]

- red blood cell (RBC) count >6.45 × 10^{12}/L
- platelets >350 × 10^{9}/L
- neutrophils >6.2 × 10^{9}/L

Absence of all criteria was effective at ruling out *JAK2* positivity with sensitivity 94.7% and negative predictive values of 98.8%. False negative rate was documented at 0.4% by using algorithm from JAKPOT study.

Upfront *BCR::ABL1* mutation screening is generally not warranted if initial evaluations, especially the full blood picture (FBP), do not strongly suggest CML. However, *BCR::ABL1* mutation screening is warranted in:[27, level III; 28, level III]

- suspected PMF patients who are negative for *JAK2, CALR*, and *MPL* driver mutations, or when trephine biopsy reveals atypical features.
- suspected ET patients who are negative for *JAK2, CALR,* and *MPL* mutations, when required to differentiate from CML.

g. Cytogenetic analysis

A retrospective cohort study prognostically assigned specific cytogenetic abnormalities into a revised cytogenetic risk stratification criteria for PMF. The findings showed:[29, level II-2]

- the three risk categories were:
  - very high risk (VHR) - single/multiple abnormalities of −7, i(17q), inv(3)/3q21, 12p−/12p11.2, 11q−/11q23, or other autosomal trisomies not including + 8/ + 9 (e.g., +21, +19)
  - favourable - normal karyotype or sole abnormalities of 13q−,

+9, 20q−, chromosome 1 translocation/duplication or sex chromosome abnormality including -Y
    - unfavorable - all other abnormalities
- VHR had the shortest median survival followed by unfavourable risk and favourable risk group (1.2 years, 2.9 years and 4.4 years, respectively)
- VHR (HR=4.4, 95% CI 2.0 to 9.4) and unfavourable risk (HR=2.0, 95% CI 1.2 to 3.4) had higher risk of leukaemic transformation compared with favourable risk group

Another retrospective cohort study looking at cytogenetic analysis of patients with PV showed:[30, level II-2]

- abnormal karyotypes were detected in 33% patients [20% in polycythemic phase (PP), 45% in post-PV MF and 90% in accelerated phase (AP)/blast phase (BP)]
- frequency of a complex karyotype increased as the disease stage advanced (1.5% in PP, 10.7% in post-PV MF and 61.5% in AP/BP)
- patients in a higher stage had a significantly inferior OS
- PP and post-PV MF patients with an abnormal karyotype showed a significantly
    - inferior OS
    - shorter transformation-free survival
- the karyotypes were grouped into three risk groups:
    - low-risk: normal karyotype, sole +8, sole +9 and other single abnormalities
    - intermediate-risk: sole del(20q), double abnormalities (including +1q)
    - high risk: complex karyotypes
- patients with low-, intermediate- and high-risk cytogenetics had a significantly different OS, with a median OS of -
    - 169, 86, and 9 months, respectively in patients in PP stage
    - 83, 46 and 24 months, respectively in patients in post-PV MF stage

Recommendation 1

- Diagnostic criteria for myeloproliferative neoplasms (MPNs) should fulfill the requirements of the World Health Organization (WHO) 2022 classification.
- Serum lactate dehydrogenase (LDH) should be performed for the diagnosis of post-essential thrombocythaemia myelofibrosis (post-ET MF) and prefibrotic/fibrotic stages of primary myelofibrosis (PMF).
- Molecular test for *JAK2* V617F should be performed at diagnosis on all patients suspected with MPNs:
    - if *JAK2* V617F is negative in patients suspected with polycythaemia vera, molecular test for *JAK2* exon 12 mutation may be considered
    - if *JAK2* V617F and *CALR* are negative in patients suspected with essential thrombocythaemia or PMF, molecular test for *MPL* mutation may be considered

2.3. Assessment of Symptom Burden

MPN symptoms can be bothersome for both patients and clinicians. Monitoring of these symptoms throughout the treatment journey is important. It is essential to have an objective tool to assess control of the symptoms as well as monitoring disease progression, with or without treatment.

a. Myeloproliferative Neoplasm - Symptom Assessment Form

An international survey to validate Myeloproliferative Neoplasm - Symptom Assessment Form (MPN-SAF) in assessing symptoms burden among MPN patients showed:[31, level III]

- acceptable consistency and correlations between symptoms burden assessment with the other established assessment tools [MPN-SAF, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and Brief Fatigue Inventory (BFI)]
- patients with MF suffered from most symptom burden while those with ET had the least symptoms
- fatigue (as measured by BFI) was the most common symptom (93%) and had the highest average severity of all reported symptoms
- MF patients had significantly more abdominal symptoms (pain/ discomfort) compared with both ET and PV patients

b. Myeloproliferative Neoplasm - Symptom Assessment Form Total Symptoms Score

An International prospective survey on Myeloproliferative Neoplasm - Symptom Assessment Form Total Symptoms Score (MPN-SAF TSS) in assessing symptom burden in MPN patients demonstrated that MPN-SAF TSS was a useful and reliable tool in evaluating treatment response and tracking disease progression.[32, level III]

- Assessment of symptoms related to MPN is important in the management of the disease.

3. TREATMENT

Patients with MPNs require individualised management plans due to varying effects of treatment response on them. Research is still limited for this relatively uncommon disease but will continue to develop as new therapies are added to the growing armamentarium. Treatment options range from lifestyle changes, venesection and splenectomy, to the latest tyrosine kinase inhibitors and stem cell transplant. Each type of MPN should be managed holistically, involving regular discussions with patients and family members to minimise symptoms, prolong life and address adverse events (AEs) from the chosen management strategy.

3.1. Risk Stratification Criteria

MPN patients may develop morbidity from the diseases and sustain poor QoL. Hence, risk stratification is needed to determine the treatment strategy and modify the disease outcomes and, these are discussed below. Risk stratification criteria will evolve in view of new information on molecular mutation, etc. However, the existing criteria are useful to guide healthcare providers on the selection of treatment.

a. Polycythaemia vera

A Korean National Guideline 2020 recommends risk stratification for PV (refer to **Table 1**).[33, level III]

Table 1: Risk stratification for PV

Risk	Attributes
Low	Age <60 years old and no prior history of thrombosis
High	Age ≥60 years old or prior history of thrombosis regardless of other factors

Adapted: Kim SY, Bae SH, Bang SM, et al. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. Korean J Intern Med. 2021;36:45-62.

b. Essential thrombocythaemia

The above Korean guideline recommends risk stratification for ET based on revised-IPSET-thrombosis (r-IPSET-t) as shown in **Table 2**.[33, level III]

Table 2: Risk stratification for ET (revised IPSET-t)

Risk	Attributes
Very low	Aged ≤60 years old, negative *JAK2* mutation and no prior thrombosis
Low	Aged ≤60 years old, positive *JAK2* mutation and no prior thrombosis
Intermediate	Aged >60 years old, negative *JAK2* mutation and no prior thrombosis history
High	Aged >60 years old and positive *JAK2* mutation or prior thrombosis history

Adapted: Kim SY, Bae SH, Bang SM, et al. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. Korean J Intern Med. 2021;36:45-62.

Despite *JAK2* mutation being a criterion in risk stratification of ET, other mutation may be important to be considered. In a meta-analysis of five prospective and two retrospective cohort studies among patients with ET comparing between *MPL* vs *JAK2* V617F mutation, thrombotic events were found to be higher in *MPL* (RR=1.80, 95% CI 1.08 to 3.01).[34, level II-2]

In a retrospective cohort study comparing revised version of International Prognostic Score for Thrombosis in Essential Thrombocythaemia-thrombosis (r-IPSET-t) and International Prognostic Score for Thrombosis in Essential Thrombocythaemia-thrombosis (IPSET-t) as prognostic score for thrombosis in ET, r-IPSET-t score was more predictive for thrombotic risk stratification.[35, level II-2]

c. Primary myelofibrosis

For PMF risk stratification, the following has been recommended and which has also been illustrated in **Table 3**:[36; 37]

- IPSS and DIPSS are calculated to stratify PMF into low, intermediate-1, intermediate-2 and high risk
- IPSS is used at the time of diagnosis while DIPSS can be applied during follow-up
- DIPSS-plus can be used if recent karyotyping is available. DIPSS must be calculated first to get the risk group. One point each is then added for three additional variables

Table 3: Risk stratification for PMF

Variables	IPSS	DIPSS	DIPSS-plus
Age >65 years old	1	1	• First determine the risk group based on DIPSS score. • Then score as follows: Low = 0, Intermediate-1 = 1, Intermediate-2 = 2, High = 3. • Lastly, add one point for each of the three additional variables below for final DIPSS-plus score risk group.
Constitutional symptom	1	1	
Hb <10 g/dL	1	2	
Leucocytes >25 x 10^9/L	1	1	
Circulating blast >1%	1	1	
Platelet count <100 x 10^9/L			1
RBC transfusion need			1
*Unfavourable karyotype			1

Risk groups	Points	Points	Points
Low	0	0	0
Intermediate-1	1	1 - 2	1
Intermediate-2	2	3 - 4	2 - 3
High	≥3	5 - 6	≥4

*Unfavourable karyotype includes +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearrangements

Abbreviation: DIPSS = Dynamic International Prognostic Scoring System; g/dL = gram per decilitre; Hb = haemoglobin; IPSS = International Prognostic Scoring System; L = litre; PMF = primary myelofibrosis; RBC = red blood cell

Adapted:

1. Gerds AT, Gotlib J, Ali H, et al. Myeloproliferative Neoplasms, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(9):1033-1062.
2. Vannucchi AM, Barbui T, Cervantes F, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v85-99.

d. Post-polycythaemia vera and post-essential thrombocythaemia myelofibrosis

Summary of Myelofibrosis Secondary to PV and ET Prognostic Model (MYSEC-PM) recommendation on risk stratification for post-PV and post-ET MF is shown below (refer to **Table 4**):[36]

Table 4: Risk stratification for post-PV and post-ET MF

Variables	Points
Hb <11 g/dL	2
Circulating blast ≥3%	2
CALR unmutated genotype	2
Platelet count <150 x 10^9/L	1
Constitutional symptom	1
Age	0.15 per year
Risk groups	**Scores**
Low	<11
Intermediate-1	11 - 13
Intermediate-2	14 - 16
High	>16

ET = essential thrombocythaemia; g/dL = gram per decilitre; Hb = haemoglobin; L = litre; MF = myelofibrosis; PV = polycythaemia vera

Recommendation 2
- Risk stratification should be performed upon diagnosis of myeloproliferative neoplasm subtypes prior to the initiation of treatment.

3.2. Non-Pharmacological Treatment

a. Therapeutic phlebotomy/venesection

Phlebotomy should be instituted in all patients with PV, regardless of risk category, with a Hct target of ≤45%.[38]

In a prospective cohort study on serial phlebotomy for patients with primary and secondary polycythaemia, rapid and marked improvement of haematological parameters, minimal AEs and significant amelioration of clinical parameters were seen as the following:[39, level II-2]

- significant decline in mean Hb from baseline of 17.84 ± 1.88 g/dL to 14.67 ± 1.14 g/dL and mean Hct from baseline of 57.11 ± 5.47% to 46.27 ± 3.763% upon achievement of desired Hct for PV and secondary polycythaemia of 45% and 52%, respectively
- significant decline in serum iron from baseline of 132.85 ± 94.136 µg/dL to 69.41 ± 58.643 µg/dL at the desired Hct level
- weakness/fatigue was seen in all patients and only one instance of pain and swelling at the phlebotomy site was reported; these symptoms did not deter patients from subsequent therapeutic phlebotomies
- significant change in visual analogue scale (VAS) score of almost all clinical parameters observed

b. Therapeutic apheresis

Therapeutic apheresis is the process of removing whole blood from the affected patients, separating out the offending cell components in an automated cell separator and returning the treated blood to patients.

i) Erythrocytapheresis

Therapeutic erythrocytapheresis is a secure strategy to achieve Hct reduction in a shorter time than phlebotomy in certain PV patients with expected haemodynamic intolerance or failure to respond to phlebotomies.

A pre-post study on patients who were not fit for phlebotomy showed that the erythrocytapheresis:[40, level II-3]

- achieved response rates in 87.5% of PV and 50% of secondary polycythaemia patients
- had AEs in only 7.1% of patients

ii) Thrombocytapheresis

In a prospective single centre cohort study on thrombocytapheresis for the prophylactic and therapeutic indications in MPN patients with platelet count >1000 x 10^9/L, the findings were:[41, level II-2]

- 73.5% of patients experienced vasomotor symptoms before apheresis with 66.9% of them achieved symptom relief
- median and mean platelet counts were significantly lower immediately, and at 24 hours after procedure
- median and mean percentage reduction of platelets were 44.5% and 41.9%, respectively
- a minimal number of patients had mild AEs; there were no severe complications attributed to the procedure

Recommendation 3

- Phlebotomy should be considered in patients with polycythaemia vera (PV).
- Erythrocytapheresis may be considered in PV patients unfit for phlebotomies.

c. Splenectomy and splenic irradiation

Splenomegaly is the hallmark of MF. The management of pre-transplant splenomegaly is crucial because significant splenomegaly is associated with a higher risk of delayed engraftment, graft failure, increased non-relapse mortality (NRM) and shorter survival after transplant.

Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation recommends considering second-line options [e.g. alternative Janus kinase (JAK) inhibitors, splenectomy, splenic irradiation or experimental strategies] for MF patients who are allo-HCT candidates with palpable spleen length >5 cm and suboptimal

response after three months of first-line JAK-inhibitor. Splenic irradiation is an alternative option for those contraindicated for surgery.[42]

In a retrospective cohort study on patients with MF and had allo-HCT, excluding those in accelerated or blast phase, the findings were:[43, level III]

- risk of mortality was lower in those with palpable spleen length ≥15 cm and underwent pre-transplant splenectomy than those without surgery (HR=0.44, 95% CI 0.28 to 0.69)
- risk of NRM was lower in those who underwent splenectomy with prior spleen size of ≥15 cm (HR=0.26, 95% CI 0.14 to 0.49) and 5 - 14 cm (HR=0.51, 95% CI 0.28 to 0.94) than those non-splenectomised
- however, risk of relapse was higher in splenectomised patients than those with palpable spleen length <5 cm (HR=2.08, 95% CI 1.21 to 3.59)

In a pre-post study of patients with MPN whom spleen size >22 cm, splenic irradiation before stem cell transplant was effective and safe with low AEs:[44, level II-3]

- Median splenic size reduction at five days and 12 months post-radiation were 7.3% (ranged 0% to 22.5%) and 14.3% (ranged 5.3% to 36.5%), respectively.
- Post-transplant neutrophil engraftment rates were 100% with a median time of 18 days (ranged 15 to 32 days).
- Radiation-related haematological toxicities were changes in Hb levels (median= -0.4 g/dL, ranged -1.9 to 0.9), platelet counts (median= -19 $x10^9$/L, ranged -108 to 31) and leucocyte counts (median= -6.35 x 10^9/L, ranged -27.9 to 1.6).
- There was no grade 3 or greater non-haematologic toxicities.

Recommendation 4

- Splenectomy or splenic irradiation may be offered in myelofibrosis patients who are candidates for allogenic haematopoeitic stem cell transplant with palpable spleen >5 cm after suboptimal response with Janus kinase inhibitor treatment.

3.3. Pharmacological Treatment

Pharmacological treatments for MPNs focus on improving symptom burden, increasing long-term survival and managing both thrombotic or bleeding complications. However, they are often limited by local drug availability, high costs and debilitating AEs. Options range from cytoreductive agents, e.g. hydroxyurea (HU), to newer targeted JAK-inhibitors, e.g. ruxolitinib and momelotinib, with manageable common AEs.

a. Antithrombotic

MPN is highly associated with a risk of thrombosis and causes substantial cardiovascular (CV) morbidity and mortality. Thus, antithrombotic is crucial to prevent these events.

i) Antiplatelet

In a small Cochrane systematic review on PV, low-dose aspirin showed a marked, but NS difference compared with placebo in the following outcomes:[45, level I]

- all-cause mortality and mortality from thrombotic events
- risk of minor and major bleeding

A systematic review on antiplatelet therapy in ET revealed insufficient evidence to conclude that its benefits outweighing the risks.[46, level II-2]

Following the evaluation of all recent evidence, it is recommended that all PV and ET patients, including those stratified as low-risk, should be given low dose aspirin if there are no specific contraindications.[33, level III; 47]

The CPG DG is of the same opinion with the most updated guidelines mentioned above.

Recommendation 5

- Aspirin should be given to all essential thrombocythaemia and polycythaemia vera patients, including those stratified as low-risk unless contraindicated.

ii) Anticoagulant

A small retrospective cohort study on oral anticoagulant in preventing recurrent arterial or venous thrombosis among patients with MPNs showed:[48, level II-2]

- venous thromboembolism (VTE) was more prevalent than arterial thromboembolism (ATE); patients with PV had the highest risk among the subtypes of MPN
- direct oral anticoagulants (DOACs) were as effective as vitamin K antagonist (VKA) in preventing recurrent ATE/VTE in MPN; incidence rate of ATE/VTE recurrences was 8.1% per patient/year in VKA-treated patients and 7.2% per patient/year in DOAC-treated patients
- risk of recurrent thrombotic events increased during and after treatment cessation in VKA-treated patients [however the documented time in therapeutic range (TTR) was 57%, which indicated VKA underdosing], while it only occurred after treatment cessation in DOACs-treated cohort
- both VKA and DOACs had comparable safety data with regard to bleeding episodes

MPN-DOACs study on thrombotic and bleeding complications in MPN patients with atrial fibrillation and/or VTE who were treated with DOACs demonstrated:[49, level II-3]

- the risk of thrombosis (first and/or recurrent events) remained high despite on DOAC
- conventional CV and atherosclerotic risk factors augmented the risk of thrombosis
- increased bleeding risk in:
  - PMF compared with other MPN phenotypes (HR=3.6, 95% CI 1.6 to 8.2)
  - dabigatran than three other DOACs (HR=3.8, 95% CI 1.5 to 9.7)

A systematic review on DOACs in MPN patients revealed an overall rate of recurrent thrombosis of 8.9% and major bleeding rate of 6.9%.[50, level II-2] In another systematic review of 10 observational studies on MPN patients with thrombosis, 60% of bleeding events occurred in those treated with antiplatelet therapy ± oral anticoagulant and mainly in the gastrointestinal system.[51, level II-2]

- The use of antiplatelet agents in conjunction with anticoagulants may increase the risk of bleeding events.

Recommendation 6

- Patients with high-risk myeloproliferative neoplasms (MPN) should be managed comprehensively concerning their cardiovascular risk in addition to antithrombotic therapy.
- Direct oral anticoagulants may be used as an alternative to prevent recurrent thrombosis in patients with MPN.

b. Hydroxyurea

HU (also known as hydroxycarbamide) is a non-alkylating anti-metabolite drug that disrupts DNA replication by inhibiting the enzyme ribonucleoside diphosphate reductase in abnormally dividing cells, making it a useful cytoreductive agent for controlling neoplastic cell counts.

- It is generally well tolerated, with AEs including gastrointestinal symptoms, myelosuppression, macrocytosis and mucocutaneous complications, e.g. mucosal ulcers and skin lesions.[47]
- HU is not safe in pregnancy and should be stopped three months prior to conception. Patients on HU should be advised about adequate contraception.[38]
- HU has been shown to have a low leukaemic and fibrotic transformation rate.[52, level III]

i) Polycythaemia vera

- HU is the first-line therapy for high-risk PV patients.[52, level III]
- PV patients treated with HU have significantly fewer vascular complications than patients on venesection alone, with a survival advantage; these support its use as a first-line agent.[47]
- HU is used in combination with anti-platelet and venesection.
- Clinicians should avoid causing side effects in efforts to achieve target platelet counts when Hct is already controlled.[52, level III]
- HU may be considered in low-risk PV patients to:[52, level III]
  - lessen phlebotomy frequency
  - treat disease-associated symptoms e.g. pruritus, splenomegaly and constitutional symptoms
  - overcome aspirin resistance patients
  - enable repletion of iron stores in patients whose symptoms are attributed to iron deficiency

In a multicentre Cytoreductive Therapy in Polycythaemia Vera (CYTO-PV) trial comparing the effectiveness of conventional treatment (phlebotomy, HU or both), low-Hct group (Hct target of <45%) had a significantly lower risk of CV-related outcomes than high-Hct group (Hct target of 45 - 50%):[53, level I]

- high-Hct group had a shorter time to death from CV causes or major thrombotic events (HR=3.91, 95% CI 1.45 to 10.53); incidence of death from CV causes or major thrombosis was 1.1 per 100 person-years in low-Hct group and 4.4 per 100 person-years in high-Hct group
- high-Hct had a higher percentage of total CV events (4.4% vs 10.9%, HR=2.69, 95% CI 1.19 to 6.12)

A change of treatment should be considered in the event of HU intolerance or resistance, as defined in **Table 8** on **Definition of Resistance/Intolerance to Hydroxyurea**. Alternatives may include phlebotomy, JAK inhibitors (e.g. ruxolitinib) and interferons (IFNs).

ii) Essential thrombocythaemia

Cytoreductive agents are not required for very low/low risk ET. However, HU is indicated for intermediate-risk and high-risk ET patients.[27, level III]

In a small meta-analysis of two randomised controlled trials (RCTs), HU compared with anagrelide in patients with ET had lower risk in the composite of all thrombosis, major bleeding and death (RR=0.78, 95 % CI 0.63 to 0.97). Analysis of specific outcomes showed:[54, level I]

- lower risk of arterial (RR=0.64, 95 % CI 0.45 to 0.90) but higher risk of venous thrombosis (RR=2.67, 95 % CI 1.26 to 6.11)
- lower risk of transformation to MF (RR=0.33, 95 % CI 0.13 to 0.83)

Risk of bias assessment showed that the primary studies had unclear and high risk of bias.

iii) Myelofibrosis

HU may be used for cell count control during the early proliferative stage of MF. However, sustained symptomatic and splenic responses are uncommon, and effective cytoreduction may be hampered by anaemia side effects. In very proliferative cases, HU may be combined with ruxolitinib.[55]

Recommendation 7

- Hydroxyurea should be used as the first-line agent for:
  - high-risk polycythaemia vera
  - intermediate- and high-risk essential thrombocythaemia

c. Interferon

Interferons have been used in the treatment of MPN, especially in PV and ET. This class of drugs is preferred in a selected group of patients for its special pharmacological properties.

A multicentre trial on pegylated interferon (PEG-IFN) among high-risk PV and ET who were intolerant or resistant to HU at 12 months showed:[56, level II-3]

- an overall response rate (ORR) of 69% (95% CI 56.6 to 80.0) and 60% (95% CI 45.2 to 73.6) in ET and PV patients, respectively
- patients with complete response had significant improvement in total symptoms score (TSS), Global Health Status/Quality of Life (GHS/QoL) score, fatigue, early satiety and itching, compared with those with partial response or no response

Myeloproliferative Disorders Research Consortium (MPD-RC) 112, a multinational RCT, comparing the effectiveness and safety of PEG-IFN vs HU in high-risk PV and ET (treatment naïve) patients at 12 months. It demonstrated:[57, level I]

- both PEG-IFN and HU achieved complete clinico-haematological response at 35% and 37%, respectively
- PEG-IFN had significantly higher haematological response (without phlebotomy) among PV patients (65% vs 43%)
- HU had significantly higher histopathological response (23% vs 5%) especially in the ET patients
- PEG-IFN had significantly higher ORR at 24 months (60% vs 41%) and sustained over 36 months
- PEG-IFN had a higher rate of *JAK2* V617F VAF allele burden reduction (-0.16 vs -0.004) at 24 months
- both therapies exhibited NS difference in spleen volume reduction (SVR) at any point during the treatment period
- incidence of grade ≥3 AEs was significantly greater with PEG-IFN (46% vs 28%)

Common AEs related to PEG-IFN were flu-like symptoms, injection site irritation, vision changes and peripheral sensory neuropathy.[57, level I; 56, level II-3] The risks could be minimised with proper patient selection, gradual dose escalation, prompt evaluation and supportive management of the AEs.

In a meta-analysis of six cohort studies and four RCTs on patients with MF treated with IFN, ORR among all studies was 49.9% (95% CI 30.4 to 69.3). It also showed a NS difference in ORR between PEG-IFN (ORR=50.0%, 95% CI 26.2 to 73.9) and non-PEG-IFN (ORR=49.6%, 95% CI 20.5 to 79.0). However, the meta-regression analysis showed discontinuation rate due to AEs was significantly higher with non-PEG-IFN (35.8%, 95% CI 3.5 to 68.1) than PEG-IFN (0.5%, 95% CI -5 to 15). The quality of primary studies was moderate.[58, level I]

A multicentre RCT using the data from PROUD-PV and its extension, CONTINUATION-PV, compared ropeginterferon alfa-2b with HU for PV patients. Although non-inferiority was not shown at 12 months in PROUD-PV, the interim analysis in the more recent study showed that the novel treatment was better in terms of:[59, level I]

- complete haematological response (RR=1.42, 95% CI 1.08 to 1.86) and molecular response (RR=1.94, 95% CI 1.38 to 2.72) at 24 months
- complete haematological response and improvement in disease burden at 36 months (RR=1.42, 95% CI 1.01 to 2.00)

Recommendation 8

- Pegylated interferon may be considered in the treatment of high-risk essential thrombocythaemia and polycythaemia vera who are intolerant or resistant to hydroxyurea.

d. Janus kinase inhibitor

The advent of targeted immunotherapy has provided patients with a more effective and less toxic treatment option than conventional anti-neoplastic chemotherapeutics. JAK inhibitors are immune-modulating drugs which inhibit the activity of the JAK family of enzymes (*JAK1, JAK2, JAK3, TYK2*), thereby interfering with the JAK-STAT signalling pathway in lymphocytes and controlling abnormal cell count levels. Although absolute cure is still in the distant horizon, JAK inhibitors e.g. ruxolitinib, fedratinib, momelotinib and other similar drugs are still in the pipeline allowing myeloproliferative patients to at least have a better QoL.

i) Ruxolitinib

Ruxolitinib is a *JAK1* and *JAK2* inhibitor that has emerged as an important therapy in managing MF, particularly for intermediate or high-risk patients. It is useful for both transplant and non-transplant eligible MF patients. Given the complex clinical heterogeneity associated with MF, therapy remains personalised, emphasising careful risk assessment prior to initiation.

- **Polycythaemia vera**

An RCT on patients with PV who had an inadequate response to or unacceptable AEs from HU, compared with standard therapy (various pharmacological agents or no medication), ruxolitinib:[60, level I]

- was more effective in composite primary end point of both Hct control and ≥35% reduction in spleen volume (SVR35) (20.9% vs 0.9%, p<0.001)
- had higher proportion ≥50% reduction in the MPN-SAF TSS (49% vs 5%)

A good meta-analysis of high quality RCTs on PV showed that ruxolitinib (starting dose of 10 mg BD with individualised dose titration ranging from 5 mg OD to 25 mg BD) had lower proportion of thrombotic events than the best available therapy (BAT) but NS.[61, level I]

Another meta-analysis of RCTs aiming to estimate risk of infections in PV patients treated with ruxolitinib 10 mg BD vs BAT, the former:[62, level I]

- had higher risk of developing herpes zoster infection (OR=7.39, 95% CI 1.33 to 41.07)
- showed NS difference in risk of serious pneumonia, fatal sepsis, grade 3 - 4 infection or any grade of infection

HU is a standard first-line treatment for PV but some patients may become intolerant or resistant to it, leading to poorer prognosis with limited options. The MAJIC-PV trial comparing ruxolitinib to BAT among PV patients who were intolerant or resistant to HU showed ruxolitinib:[63, level I]

- had higher complete response rate within 12 months by ELN criteria (OR=2.12, 90% CI 1.25 to 3.60) and was significantly associated with more durable complete response
- was superior in event free survival (HR=0.58, 95% CI 0.35 to 0.94)

More infections (e.g. respiratory, genitourinary and cutaneous herpes zoster) were seen in ruxolitinib-treated patients. However, there were no infection-related deaths or atypical infections in both groups. Eleven cases (11.6%) of squamous cell skin cancer were reported in ruxolitinib-treated patients.

- **Essential thrombocythaemia**

An open-label RCT (MAJIC-ET) evaluated activity and safety of ruxolitinib vs BAT (HU 71.1%, anagrelide 48.1% and IFN 40.4%) in patients with ET and demonstrated:[64, level I]

- NS difference in partial response and complete response, although time to first response was significantly longer for BAT (p=0.01)
- NS difference in duration of response
- similar OS and progression-free survival rates
- NS differences in transformation-free (to MF), thrombosis-free and haemorrhagic-free probability; analysis of all three probabilities as a composite endpoint was still NS
- NS difference in achieving ≥50% reduction in MPN-SAF TSS score from baseline, although there was a significantly faster reduction in symptoms score from baseline for ruxolitinib

- **Myelofibrosis**

Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT) I was a multicentre RCT evaluating the effectiveness and safety of ruxolitinib vs placebo among MF patients. It showed that ruxolitinib provided significant clinical benefits at week 24 by:[65, level I]

- higher SVR35 (41.9% vs 0.7%)
- changes in MF-related symptoms (mean improvement of 46.1% vs mean worsening of 41.8%)
- improvement of OS (mortality rate of 8.4% vs 15.6%)

In another multicentre RCT (COMFORT II) on the same outcomes comparing ruxolitinib vs BAT among MF patients, continuous ruxolitinib therapy till week 48 was associated with:[66, level I]

- significant SVR35 (28% vs 0%)
- improvement in disease-related symptoms, role functioning and QoL
- manageable non-haematological AEs e.g. diarrhoea

In both RCTs, cytopenia (mainly anaemia and thrombocytopenia) was common with ruxolitinib and appeared as early as eight weeks of therapy. It was managed with careful dose titration and/or packed cell transfusion.

ii) Pacritinib

Pacritinib primarily inhibits *JAK2* (wild-type and *JAK2 V617F*) and *FLT3*. It has a greater inhibitory potency towards *JAK2* than related proteins (e.g. *JAK3, TYK2*) and does not inhibit *JAK1* at clinically relevant concentrations. It has been approved by U.S. Food and Drug Administration for the treatment of both primary and secondary MF in patients with platelet counts <50 x 10^9/L.

In PERSIST-1 trial on MF patients, pacritinib was more effective than BAT at 24 weeks in terms of:[67, level I]

- higher SVR35 achievement (19% vs 5%, p=0.0003) including subgroup analysis of baseline platelet count of <100 x 10^9/L and <50 x 10^9/L
- NS in achieving ≥50% reduction in TSS 2.0

Most common grade 3 - 4 AEs were anaemia, thrombocytopenia and diarrhoea in pacritinib while anaemia, thrombocytopenia, dyspnoea and hypotension were seen in BAT.

In an RCT on patients with MF who had platelet <100 x 10^9/L, comparison at week 24 between pacritinib of different dosing and BAT showed the following:[68, level I]

- for SVR35, the percentages were significantly higher in pacritinib 200 mg BD and 400 mg OD than BAT (22% vs 3% and 15% vs 3%, respectively)
- for ≥50% reduction in MPN-SAF TSS 2.0, only pacritinib 200 mg BD was significantly more effective than BAT (32% vs 10%) but not for 400 mg OD
- NS difference in OS between pacritinib and BAT
- all haematologic, cardiac and bleeding AEs were similar among the groups

iii) Momelotinib

Momelotinib is a JAK inhibitor that has additional inhibition of hepcidin, thereby increasing iron availability for erythropoiesis. This makes it an alternative to MF patients who develop anaemia while on ruxolitinib.

In a double-blind phase 3 RCT [Momelotinib Versus Ruxolitinib in Subjects With Myelofibrosis (SIMPLIFY-1)] involving JAK inhibitor-naïve patients with MF comparing momelotinib vs ruxolitinib, the former showed:[69, level I]

- non-inferiority in ≥35% SVR with proportion difference in spleen response rate at 24 weeks (SRR24) of 0.09 (95% CI 0.02 to 0.16)
- non-inferiority was not demonstrated in symptomatic improvement
- improved transfusion-independence and composite clinical improvement (composite of SRR24, TSS symptoms improvement and transfusion independence)
- fewer anaemia and thrombocytopenia but higher incidence of nausea

In another open-label, phase 3 RCT [Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY-2)] involving MF patients who were on ruxolitinib but had either suboptimal responses or haematological toxic effects with ruxolitinib, comparison of momelotinib vs BAT demonstrated that the former had:[70, level I]

- NS difference of ≥35% in SRR24
- significantly more patients with ≥50% reduction in TSS scores at 24 weeks
- significantly more RBC transfusion-independence by 24 weeks
- slightly more AEs, the most common being diarrhoea, nausea, cough and dizziness and, a significantly higher proportion of peripheral neuropathy

The third double-blind, phase 3 RCT (MOMENTUM) involving MF patients who developed anaemia on a JAK inhibitor demonstrated that momelotinib, when compared with danazol, showed:[71, level I]

- significantly greater proportion of patients with ≥50% reduction in TSS scores
- non-inferiority but higher percentage in transfusion independence
- significantly higher proportion of SVR ≥25% and SVR35
- diarrhoea, nausea and asthenia were more commonly reported AEs
- NS OS

iv) Fedratinib

Fedratinib is an oral *JAK2* selective inhibitor that is a potential alternative for primary and secondary MF patients who have failed ruxolitinib. It has higher inhibitory activity for *JAK2* over ruxolitinib.

The JAKARTA trial on fedratinib (500 mg and 400 mg) vs placebo involving JAK2 inhibitor naïve MF patients showed:[72, level I]

- significant SVR35 at 24 weeks; 40% (500 mg) and 36% (400 mg) vs 1% (placebo)
- significant TSS reduction; 49% (500 mg) and 47% (400 mg) vs 1% (placebo)
- NS changes in *JAK2* allele burden in all arms
- most common non-haematological AEs were diarrhoea, nausea and vomiting, while most common haematological AEs were anaemia, thrombocytopenia and leucopenia
- three patients had confirmed Wernicke encephalopathy and one patient with unknown encephalopathy, leading to early termination of this trial on November 2013; later it was concluded that these were due to poor nutritional status and use of 500 mg dosing

An updated analysis of a single-arm fedratinib phase 2 study (JAKARTA-2) on MF patients who failed ruxolitinib (that was terminated early due to concerns of Wernicke encephalopathy) that divided study participants into three groups with stricter selection criteria [intention-to-treat (ITT), stringent criteria cohort (SCC) and sensitivity analysis cohort (SAC)] showed:[73, level II-2]

- modest SVR35 – ITT at 31% (95% CI 22 to 41), SCC 30% (95% CI 21 to 42) and SAC 36% (95% CI 25 to 49)

- modest improvement in TSS – ITT 27% (95% CI 18 to 37), SCC 27% (95% CI 17 to 39) and SAC 32% (95% CI 21 to 45)
- most common non-haematologic AEs were diarrhoea (62%), nausea (41%) and constipation (21%) while most common haematological AEs were anaemia (49%) and thrombocytopenia (27%); no reports of Wernicke encephalopathy

Recommendation 9
- Ruxolitinib:
  - should be considered in treating intermediate and high-risk myelofibrosis (MF)
  - may be considered as alternative for hydroxyurea-intolerant polycythaemia vera
- Other Janus Kinase inhibitors may be considered as an alternative to ruxolitinib in MF patients who have either:
  - shown suboptimal responses
  - failed to achieve reduction in transfusion burden

e. Anagrelide

Anagrelide is a phosphodiesterase inhibitor that blocks maturation of megakaryocytes, thus having a cytoreductive role in ET and preventing its accompanying thrombotic complications. AEs include anaemia, headaches, cardiac toxicity and progression to MF, with a higher incidence of thrombo-haemorrhagic events, leading to anagrelide being relegated to a second-line option or as an add-on for those who are refractory or intolerant to first-line therapies. It is non-leukaemogenic and does not impair fertility but has teratogenic effects. Monitoring must also be done for fibrotic progression.[2]

The meta-analysis of two RCTs which compared the safety between anagrelide and HU among ET patients showed that anagrelide was better in terms of incidence of venous thrombosis but not in arterial thrombosis, major bleeding and total bleeding. There were NS difference in overall incidence of thrombosis and death.[54, level I]

A non-inferiority RCT comparing the effectiveness, safety and tolerability of short-term to long-term anagrelide treatment against HU among high-risk ET patients showed that anagrelide had:[74, level I]
- non-inferiority in means of platelet counts at six months (MD= -45.5 x 10^9/L, 95% CI -96.66 to 5.71)
- similar proportion of patients with complete response (58.9% vs 58.8%) but lower proportion of partial response at six months (21.9% vs 27.9%)
- longer time to complete response (177.0 days vs 123.0 days) and complete/partial response (61.0 days vs 47.0 days)

- NS different in the effect of left ventricular ejection fraction
- similar proportion of patient with treatment-emergent AEs; however, higher proportion of disease-related thrombotic or haemorrhagic events (41.1% vs 23.5%)

In another pre-post study (Study 308) assessing the effectiveness and safety of anagrelide treatment among high-risk Japanese patients with ET who were intolerant or refractory to cytoreductive therapy, about 67.9% responded (platelet count ≤600 x 10^9/L), 45.3% achieved normalisation of platelet (platelet count ≤400 x 10^9/L) and 50.9% achieved 50% reduction of platelet counts after 12 months of anagrelide.[75, level II-3] The reduction of platelet counts was sustained even until 48 months as reported in the continuation study (Study 309).[76, level II-3]

However, both the above studies had demonstrated that all patients receiving anagrelide reported at least one treatment-emergent AEs with majority of them having mild to moderate AEs. The most common AEs were anaemia, headache, palpitations, nasopharyngitis, diarrhoea and peripheral oedema.[75, level II-3; 76, level II-3]

- All patients initiated on anagrelide must have a routine chest radiograph and electrocardiogram, proceeding to echocardiogram if they show any abnormalities or have past cardiac history.

f. Busulfan

The latest clinical updates recommend that busulfan remains as one of the second-line therapy after HU failure for ET patients >65 years old[27, level III] and PV patients >75 years old.[77, level III] The dosage is 2 - 4 mg/day and to withhold once platelets <200 x 10^9/L or WBC <3 x 10^9/L. Upon resumption, busulfan dose is reduced to 2 mg/day. Favourable outcome is seen in busulfan with higher first remission duration, higher overall 10-year survival rates and low risk of leukaemic transformation.[78, level III]

Potential AEs of busulfan include long-lasting myelosuppression, pulmonary fibrosis and teratogenicity.[77, level III] Concerns of leukaemic transformation are largely based on anecdotes, and safety of busulfan has been proven from low-level of evidence.[78, level III]

3.4. Treatment for Emergency Cytoreduction

The myeloproliferative nature of PV and ET poses a high thrombotic risk, more often venous than arterial. The clonal proliferations are usually erythrocytosis and thrombocytosis, but there may sometimes be hyperleukocytosis in PV. Those at increased risk for thrombosis should be identified early on (refer to **Subchapter 3.1** on **Risk Stratification**) and started on appropriate prophylaxis.

Despite best efforts to mitigate such risks, MPN patients may still present to the emergency department with thrombotic events e.g. DVT, PE, MI or ischaemic stroke. When they present as such, the initial management should focus on the thrombosis itself (e.g. thrombolysis for ST-segment elevation MI and unstable PE, triple therapy for acute coronary syndrome, anticoagulation for PE and DVT, etc.).

Once patients have been stabilised, the attending doctor can move on to rapid cytoreductive therapies which are usually a combination of various modalities. A referral to a haematologist should be considered for further management. Primary options available include haemodilution with intravenous fluids, emergency venesection (refer to **Subchapter 3.2** on **Therapeutic phlebotomy/venesection**) and drugs e.g. HU (refer to **Subchapter 3.3** on **Hydroxyurea**) or IFN (in MPN patients who are pregnant or in the reproductive age, refer to **Chapter 4** on **Treatment for Pregnant Women**).[2, level III]

In PV, erythrocytapheresis may be considered in haemodynamically unstable patients where large volume venesection is contraindicated. It can also be used when elective pre-operative cytoreduction has failed or for emergency pre-operative preparation of PV patients.[79]

In ET, thrombocytapheresis may be used for uncontrolled thrombocytosis during an acute thrombotic event, prior to urgent surgery or pregnant women with ET who have a high risk for foetal loss.[79]

Leucocytapheresis may be offered in hyperleucocytosis (WBC count of >100 x 10^9/L), especially if there are complications e.g. renal, cerebral and pulmonary stasis, or even priapism. Some studies have shown a reduction in early mortality, but none have shown any benefit to long-term survival.[79]

- A referral should also be made to the haematologist if patients are indicated for apheresis, especially if they are experiencing hyperviscosity symptoms due to high cell counts.[2, level III]

3.5. Stem Cell Transplant

In the recommendation of previous guidelines in 2004 and in the era of JAK inhibitors, allo-HCT remains the only curative treatment for patients with MF. The American Society for Transplantation and Cellular Therapy (ASTCT) considers an allo-HCT the “standard of care with clinical evidence” for patients with intermediate and high-risk disease.[80, level III]

The indications for transplant in MF patients as per European Society for Blood and Marrow Transplantation (EBMT) guidelines are:[55]

- all patients with intermediate-2 or high-risk disease according to IPSS, DIPSS or DIPSS+, and aged ≤70 years
- all patients aged <65 years with intermediate risk-1 disease if they present with either refractory, transfusion-dependent anaemia or PB blasts >2%, or adverse cytogenetics

Other patients for the consideration of transplant are those in the intermediate-1 risk group who are triple negative and/or *ASXL1* mutation positive.

The findings in a retrospective registry-based cohort study by the EBMT on patients with MF who underwent allo-HCT were:[81, level II-2]

- projected median survival was 5.3 years (95% CI 4.1 to 6.6)
- estimated survival rate at five years was 50%
- disease progression or relapse at five years occurred in 26% of patients
- graft failure was noted in 11% of patients
- 46% had acute graft-vs-host disease (aGVHD) (grades III - IV, 14%)
- 42% had chronic graft-vs-host disease (cGVHD) (extensive, 24%)

Factors independently associated with increased mortality were age ≥60 years at transplantation (HR=1.45, 95% CI 1.30 to 1.61), grades III - IV aGVHD (HR=2.95, 95% CI 2.59 to 3.36), graft failure (HR=2.30, 95% CI 1.98 to 2.68) and disease progression/relapse (HR=3.78, 95% CI 3.33 to 4.28).

A retrospective study of the EBMT registry cohort compared ruxolitinib vs no ruxolitinib prior to allo-HCT. The findings were:[82, level II-2]

- among those with ruxolitinib, there were almost equal numbers on those with ongoing spleen response and without response
- event-free survival (EFS) for entire study population at two years was 56.5% (95% CI 52.3 to 60.8); it was significantly improved in ruxolitinib patients with ongoing spleen response (68.9%) vs those without spleen response (49.9%) or those without ruxolitinib pretreatment (53.7%)
- cumulative incidence of NRM at one year was 21.9% (95% CI 18 to 25); the only significant factor for a higher NRM was human leucocyte antigen (HLA)-mismatched donor (HR=2.79)
- OS for the entire study population at two years was 63.2% (95% CI 55.0 to 66.6)
    - NS difference between ruxolitinib vs no ruxolitinib pretreatment, ongoing spleen response vs without response, and ongoing spleen response vs no ruxolitinib
    - the only significant factors for worse OS were age ≥58 years (HR=1.42) and HLA-mismatched donor (HR=2.37) after adjusted to spleen response

- incidence of aGVHD grade II - IV for the entire study population was 28.9% (95% CI 25.1 to 32.8) and showed NS difference between ruxolitinib vs no ruxolitinib pretreatment or ongoing spleen response vs without response
- cumulative incidence of overall cGVHD at two years for the entire study population was 46.7% (95% CI 42.2 to 51.2)
- for the entire study population, 31.7% experienced cytomegalovirus (CMV) reactivation after stem cell transplantation
- cumulative incidence of relapse at two years for the entire study population was 16.3%
- ongoing spleen response vs no ruxolitinib pretreatment showed HR of 0.34 (95% CI 0.12 to 0.95); it was the only significant factor in reduction of relapse

In a multicentre phase II trial on allo-HCT eligible patients with MF, ruxolitinib was given for six months before transplant. The findings were:[83, level II-1]

- for pre-transplant outcomes:
  - 26% of patients had partial remission, 20% of patients had spleen response and the remaining patients (54%) had no response to ruxolitinib at three months
  - among those with donors, 29.7% underwent a splenectomy before a scheduled transplantation
- for post-transplant outcomes:
  - all had successful engraftment at four months and one patient had late rejection
  - 2-year OS was 59% with splenectomy and 49% without splenectomy; splenectomy was not significantly associated with mortality
  - disease-free survival (DFS) was 46% (95% CI 33 to 58) at 24 months after transplantation; it was 77%, 36% and 23% for matched sibling donor (MSD), matched unrelated donor (MUD)10/10 and MUD9/10, respectively
  - cumulative incidence of grade II - IV aGVHD was 32% (95% CI 21 to 44) for all patients; it was 22% after MSD, 33% after MUD10/10 and 46% after MUD9/10
  - cumulative incidence of cGVHD was 37% (95% CI 24 to 60) at 24 months
  - NRM was 46% at 24 months; it was higher among unrelated transplant (23% after MSD vs 50% after MUD10/10 and 77% after MUD9/10, p=0.014)

As there is no standard prognostic system available in MF patients undergoing allo-HCT, a simple prognostic system using available variables is needed. A retrospective study used the disease, patient and transplantation variables data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to develop

a scoring system. It was then validated using the EBMT registry cohort to assess the outcome in patients undergoing allo-HCT for MF. The proposed scoring was as below:[84, level II-2]

Variables	Score
Age	
≤50 years	0
>50 years	1
Haemoglobin before allo-HCT	
≥100 g/L	0
<100 g/L	2
Donor type	
HLA-identical siblings	0
Well-matched UD	1
Partially matched UD	2

The 3-year OS in CIBMTR patients with low (1 - 2 points), intermediate (3 - 4 points) and high score (5 points) were 69% (95% CI 61 to 76), 51% (95% CI 46 to 56.4) and 34% (95% CI 21 to 49), respectively. Increasing score was predictive of increased transplant-related mortality (TRM) (p=0.0017) but not relapse (p=0.12). The derived scoring system from CIBMTR was predictive of OS (p<0.001) and TRM (p=0.002) but not relapse (p=0.17) in the EBMT cohort. It was concluded that the proposed system is prognostic of survival and can be easily applied by clinicians consulting patients with MF about transplantation outcomes.[84, level II-2]

- Early referral should be made for transplant counselling and preparation if the patients are deemed suitable for transplant.

Recommendation 10

- Allogeneic haematopoietic stem cell transplant may be considered for intermediate and high-risk myelofibrosis (MF) patients.
- Achieving spleen volume reduction in MF patients who are eligible for transplant, either by pharmacological or non-pharmacological methods, should be aimed for a favourable transplant outcome.

4. TREATMENT FOR PREGNANT WOMEN

MPN among women in reproductive age are increasingly being identified.[85, level II-2] Pregnancy with MPN is associated with maternal thrombosis, haemorrhage and placental dysfunction leading to foetal growth restriction, low birth weight, pregnancy loss or pre-term delivery. Hence, the management requires a multidisciplinary approach to optimise the outcomes.

a. Pre-pregnancy care

Patients with MPN need to have pre-pregnancy care and disease management optimised before conception. The European Society of Medical Oncology Guideline 2015 recommends counselling about thrombosis risk and considering thromboprophylaxis if the fertility treatment requires short-term hormonal manipulation.[37]

- HU and anagrelide should be avoided in MPN patients planning for pregnancy following careful counselling on the potential risks and benefits.

b. Antenatal and intrapartum care

Women with MPN should be managed by a multidisciplinary team involving experienced obstetricians and haematologists. The European Society of Medical Oncology Guideline 2015 recommends serial foetal growth monitoring be carried out at 20, 26 and 34 weeks with uterine arterial Doppler done at 20 weeks.[37] Another guideline also recommends that all women should receive aspirin unless contraindicated, with additional treatment for high-risk pregnancy including cytoreductive therapy with IFN and/or low molecular weight heparin (LMWH) (refer to **Table 5**).[38]

Local protocol for the interruption of LMWH during labour should be adhered to and dehydration is to be avoided.[37] Peripartum bleeding and bleeding risk can be managed in accordance with Training Manual on Management of Post-partum Haemorrhage (PPH) 2016.[86]

A meta-analysis among pregnant women with MPN using multiple interventions showed:[87, level II-2]

- higher odds of live birth in aspirin vs observation alone (OR=8.55, 95% CI 4.03 to 18.12)
- higher odds of live birth in IFN vs observation alone (OR=9.72, 95% CI 2.31 to 41.01)
- higher odds of live birth in aspirin + heparin vs observation alone (OR=16.71, 95% CI 2.83 to 98.78)
- NS difference of live birth between aspirin + heparin vs heparin alone
- NS maternal or other foetal AEs for aspirin or IFN

i) Polycythaemia vera

The British Society for Haematology Guideline 2018 recommends that Hct should be kept within the normal range for gestation with venesection and to consider IFN if venesection fails or is not tolerated in PV patients. Unnecessary iron supplementation should be avoided in the absence of proven iron depletion. If supplementation is indicated, this should be at a low dose with regular iron monitoring. If the mean pulsatile index is >1.4 during uterine doppler at 20 weeks, the frequency of growth scans should be increased and treatment escalated to include IFN and LMWH.[38]

The guidelines recommends antenatal management based on risk stratification as shown in **Table 5**.[38]

A retrospective cohort study among pregnant PV patients on PV-specific therapies (aspirin, LMWH, IFN or any combination) vs no PV-specific therapy showed that:[88, level II-2]

- live birth rate was higher with PV-specific therapies (69.0% vs 8.3%, p<0.001)
- NS difference on overall maternal pregnancy complications except an increased risk of bleeding in PV-specific therapy (p=0.021)

Intrapartum prevention of thromboembolism includes good hydration and active management of third stage of labour. Thromboembolism deterrent stockings are advisable during labour and post-partum if immobile.[38]

ii) Essential thrombocythaemia

Risk of both maternal and foetomaternal thrombotic complications increased with *JAK2* mutation. Aspirin may be necessary for high-risk women with a previous history of thrombotic complications during pregnancy.[33, level III]

A systematic review of retrospective cohort studies on pregnant women with ET using LMWH prophylaxis vs non-LMWH treatment (aspirin, IFN or PEG-IFN) showed that LMWH prophylaxis was more effective in terms of:[89, level II-2]

- proportionally lower absolute risk of VTE in the antepartum (0%, 95% CI 0.0 to 5.7 vs 2.5%, 95% CI 1.3 to 4.3) and post-partum (0%, 95% CI 0.0 to 4.6 vs 4.4%, 95% CI 1.2 to 9.5) periods
- proportionally lower bleeding risk in the antepartum period (0%, 95% CI 0.0 to 5.7 vs 4.0%, 95% CI 1.5 to 7.8)

A retrospective cohort study among high-risk pregnant patients with ET using IFN showed that:[90, level II-2]

- live birth was higher in patients on IFN compared with those without (73.5% vs 60%)

- live birth rate was significantly higher in combination therapy (i.e. triple therapy, IFN + aspirin and IFN + LMWH) than IFN alone
- NS difference in live birth rate between PEG-IFN and standard IFN alpha (IFN-α)
- NS association between *JAK2*-mutational status and pregnancy outcomes
- NS association between platelet counts and pregnancy outcomes
- no fatal maternal events reported and all AEs were manageable

c. Post-natal care

Recommendations for management of post-natal MPN care are shown in **Table 5**.

In PV, Hct should be maintained <45%. In ET, rebound thrombocytosis may necessitate cytoreductive therapy.[38]

Table 5: Management of risk factors during pregnancy for MPN

Risk factor	Antenatal	Post-natal
High risk pregnancy		
• Previous history of arterial thrombosis due to PV	• Commence IFN • Prophylactic dose LMWH twice daily • Aspirin	• Reduce LMWH to once daily prophylactic dose for 6 weeks • Aspirin • Decision to continue IFN based on individua patient discussion
• Previous history of venous thrombosis due to PV, previous pregnancy complications (>3 first trimester loss, >1 third trimester loss, birth weight <5th centile of gestation, intrauterine death or stillbirth, pre-eclampsia	• Commence IFN • Prophylactic dose LMWH once daily, then consider to increase the dose twice daily from 16 weeks onwards until delivery • Aspirin from confirmation of pregnancy	• Continue once daily prophylactic dose LMWH until 6 weeks • Aspirin • Decision to continue IFN based on individual patient discussion
• Previous history of haemorrhage due to PV or significant antepartum or postpartum haemorrhage requiring transfusion	• Commence IFN • Addition or continuation of aspirin to be decided on patient-specific basis	• Continue aspirin • Once daily prophylactic dose LMWH for 6 weeks • Decision to continue IFN based on individual patient discussion

Risk factor	Antenatal	Post-natal
• Thrombocytosis, platelet count >1500 x 10^9/L before or during pregnancy and/or diabetes mellitus or hypertension requiring pharmacological treatment	• Commence IFN • Continue aspirin	• Continue once daily prophylactic dose LMWH until 6 weeks • Aspirin • Decision to continue IFN based on individual patient discussion
Standard risk pregnancy		
All other pregnancies	• Commence aspirin	• Commence once daily prophylactic dose LMWH for 6 weeks • Aspirin

IFN = interferon; LMWH = low molecular weight heparin; MPN = myeloproliferative neoplasm; PV = polycythaemia vera

Adapted: McMullin MFF, Mead AJ, Ali S, et al. A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis: A British Society for Haematology Guideline. Br J Haematol. 2019;184(2):161-175.

Breastfeeding is safe with low-dose aspirin, heparin and warfarin, while cytoreductive therapy is contraindicated. Decisions about breastfeeding while taking IFN should be individualised.

For family planning, coated intra-uterine devices or oral contraception progesterone-only preparation are recommended. However, combined oral contraceptive (both progesterone and oestrogen) is not recommended due to the risk of thrombosis.[37]

Recommendation 11
- A multidisciplinary approach should be implemented throughout antenatal care of women with myeloproliferative neoplasms (MPNs).
- All women with MPNs should be given pre-pregnancy counselling prior to conception.
- All pregnant women with MPNs should be prescribed with aspirin unless contraindicated; its combination with low molecular weight heparin and/or interferon is preferred in high-risk patients.

5. COMPLEMENTARY INTERVENTION

Complementary intervention has been used in the treatment of MPN.

a. Diet

In a large prospective cohort study of older individuals in the National Institutes of Health-American Association of Retired Persons cohort, those who consumed high levels of sugar (>117.73 g/day) g/day were at risk of developing PV (HR=1.77, 95% CI 1.12 to 2.79). However, intake of fat and protein did not appear to influence PV risk.[91, level II-2]

In an RCT on educational dietary intervention among patients with MPN, there was an increasing percentage of participants achieving >50% reduction of MPN-SAF TSS in those who were on a longer duration of Mediterranean or U.S. Dietary Guidelines for Americans (USDA) diet. Further analysis showed:[92, level I]

- significantly modest negative correlation between Mediterranean Diet Adherence Screener (MEDAS) score and MPN-SAF TSS score
- dietary intervention was safe

b. Supplementation

In a large international survey of integrative medicine among MPN patients, those who consumed omega-3 fatty acid supplementation had significantly lower mean MPN-SAF TSS and BFI scores compared with those who did not. Supplementation with vitamin D, multivitamin, magnesium and calcium did not correlate with symptom burden, QoL, depression or fatigue.[93, level III]

c. Yoga

In a pilot RCT on MPN patients randomised to online yoga or wait-list demonstrated that the former had small to moderate improvements in sleep disturbance, pain intensity, anxiety and depression.[94, level I]

- There is limited role of complementary interventions in the treatment of MPN.

6. REFERRAL AND FOLLOW-UP

6.1. Referral

Given the potential serious complications of MPN, timely referral to haematologists is crucial for optimal management and outcomes for the patients. There is limited evidence on the referral criteria of MPN. Thus, the CPG DG writes this section based on their expert opinion with consideration of the local setting. This section outlines the key referral criteria to facilitate the effective transition of MPN patients from primary to specialised care.

a. Abnormal full blood count

The referral criteria are based on the abnormal FBC, either polycythaemia, thrombocytosis and/or anaemia. Elevated Hb/Hct and thrombocytosis have a wide differential diagnosis. The decision to refer for venesection or cytoreductive therapy in a patient depends on the underlying cause, associated symptoms and thrombotic risk factors. Anaemia may be the only clinical feature of MF at initial presentation. The patient's symptoms and initial FBC findings, particularly the mean corpuscular volume (MCV) and FBP, will influence both the urgency and direction of initial clinical investigation.[95, level III]

The referral criteria for MPN patients based on the urgency of the referral is shown in **Table 6**.

Table 6: Key referral criteria for MPN patients

Type of referral	Polycythaemia	Thrombocytosis	Anaemia
Urgent	• Extreme raised Hct >60% • Persistently raised Hct >49% in association with recent arterial or venous thrombosis, neurological symptoms, visual loss or abnormal bleeding	• Platelet count >1,000 x 10^9/L • Platelet count 600 - 1,000 x 10^9/L in association with recent arterial or venous thrombosis, neurological symptoms or new abnormal bleeding	• Unexplained progressive symptomatic anaemia • Anaemia in association with splenomegaly, lymphadenopathy or other cytopaenias
Non-urgent	• Elevated Hct (male >49%, female >48%) in association with past history of arterial or venous thrombosis, splenomegaly, pruritus, elevated WBC or platelet counts • Persistent (>3 months) unexplained elevated Hct (male >49%, female >48%)	• Persistent (i.e. lasting >6 months) unexplained thrombocytosis >450 x 10^9/L	• Persistent unexplained anaemia

Abbreviation: Hct = haematocrit; L = litre; MPN = myeloproliferative neoplasms; WBC = white blood cell

Cases not meeting the referral criteria should be managed in primary care and monitored, as outlined in **Table 7**.

Table 7: Monitoring of polycythaemia, thrombocytosis and anaemia in primary care settings

Polycythaemia	Thrombocytosis	Anaemia
• Serial FBCs (non-fasting blood samples with patient in well-hydrated state) • FBP - indicated for Hct >52% (males) or >49% (females) on second presentation • Modify known associated lifestyle factors: smoking, alcohol, diuretics and SGLT2 inhibitors • Screen for diabetes mellitus	• FBP - indicated for persistently elevated platelet count >450 x 10^9/L (for ≥6 months) • Investigate and treat secondary causes: ○ Ferritin and iron studies - iron deficiency ○ Elevated CRP/ESR - reactive thrombocytosis ○ Rule out infection, inflammation or neoplasia	• Detailed history - focus on duration, symptoms, bleeding, diet, drug and family history • FBP and reticulocyte count • FBP - indicated for: ○ first Hb <8.5 g/dL OR ○ Hb <10g/dL if RDW >17% in the presence of reticulocytosis • Ferritin, B12 and folate, serum iron, TIBC, transferrin saturation (this will be more informative than ferritin if there is an inflammatory component) • Serum immunoglobulins and protein electrophoresis • Renal and liver biochemistry • Monitor FBC for evidence of progression over time

Abbreviation: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FBC = full blood count; FBP = full blood picture; g/dL = gram per decilitre; Hb = haemoglobin; Hct = haematocrit; L = litre; RDW = red cell distribution width; SGLT2 = sodium-glucose co-transporter 2; TIBC = total iron binding capacity

b. Presence of clinical symptoms and signs

The CPG DG opines that the following features should be included in the referral criteria:

- splenomegaly - physical examination revealing an enlarged spleen should prompt further diagnostic evaluation
- microvascular symptoms - patients presenting with erythromelalgia,

headache, dizziness, or visual disturbances that cannot be explained by other conditions may be experiencing symptoms of blood hyperviscosity or microvascular circulation issues
- thrombotic or haemorrhagic events - history of unprovoked thrombosis at unusual sites or bleeding tendencies may indicate an underlying MPN
- uncertain or progressive clinical course - patients with inexplicable progression in blood counts or evolving symptoms despite treatment for assumed secondary causes should be referred for a specialist's evaluation

c. Genetic Testing

The CPG DG opines that if *JAK2* V617F mutation testing is available and the result is positive, the patient should be referred to haematology services. Other genetic markers like *CALR* or *MPL* mutations in the setting of suggestive hematologic findings also guide referrals.

- Effective communication between primary care physicians and haematologists is essential in the referral process. When referring a patient, it is important to provide:
  - a complete medical history, including symptom onset and evolution
  - detailed blood counts over time, including trends and any exacerbating factors (e.g. infection, active bleeding)
  - results of any prior investigations, including genetic tests
  - information on any prior thrombotic or haemorrhagic events
  - notes on any relevant family history of haematologic disorders

Recommendation 12
- Patients presenting with the following criteria should be referred urgently to haematology services:
  - extreme raised haematocrit (Hct) (male >60%, female >56%) in the absence of congenital cyanotic heart disease
  - persistently raised Hct (male >49%, female >48%) in association with recent arterial or venous thrombosis, neurological symptoms, visual loss or abnormal bleeding
  - platelet count >1000 x 10^9/L
  - platelet count 600 - 1000 x 10^9/L in association with recent arterial or venous thrombosis, neurological symptoms or new abnormal bleeding

6.2. Monitoring

Treatment in MPN aims to reduce symptom burden, risk of leukaemic transformation and risk of thrombosis/bleeding. The course of

treatment presents challenges; therefore, monitoring is crucial in managing disease progression, evaluating treatment effectiveness and enhancing patient outcomes. This process involves a combination of clinical, haematological, molecular and radiological assessments, all aligned with established international guidelines.[37; 96; 97] Clinical evidence supports a multifaceted approach to monitoring these disorders, ensuring personalised care is adapted to each patient's unique disease profile and response to treatment.

Patients with PV and ET on stable doses of cytoreductive agent(s) can be discharged to the nearest primary care clinic if deemed suitable. They will be followed up based on clinical, biochemical and radiological assessment between 3- to 6-monthly. Communication with haematologists is encouraged when a patient develops new symptom(s), abnormal biochemical and haematological tests. Referral to be made if it fulfils the criteria as illustrated in **Subchapter 6.1** on **Referral**.

AML or MF transformation warrants early detection of clinical features including worsening cytopenia, increased PB blast and persistently raised LDH. Further laboratory assessment is required to confirm this transformation.

- Long-term monitoring is essential for the management of MPNs due to their chronic nature and the possibility for disease progression or complications. Regular monitoring facilitates:
  - assessment of clinical response through haematological and symptom control
  - early detection of disease progression via haematological and molecular testing,
  - optimisation of treatment strategies guided by serial clinical and biochemical evaluations.

a. Clinical

Clinical assessment can be conducted through symptoms and signs exhibited by patients during each consultation. The MPN-SAF and MPN-SAF TSS are two validated scoring systems in monitoring patients with MPN. They effectively address both the physical symptoms and psychosocial aspects of the disease.

The NCCN and ELN guidelines suggest that microvascular complications and major vessel thrombosis should be systematically assessed. Risk stratification models, which consider factors e.g. age, previous thrombosis and cardiovascular risk factors, are used to tailor cytoreductive and antithrombotic strategies.[96; 97]

The BSH emphasises risk of opportunistic infections in patients receiving ruxolitinib. It is advised to assess hepatitis B and C, as well as human immunodeficiency virus (HIV) status before initiating treatment. Additionally, evaluating risk factors for mycobacterial infections and herpes zoster reactivation is recommended.[55]

b. Haematological and biochemical

The FBC remains a fundamental tool in haematological monitoring and should be complemented by blood film and/or bone marrow examination when indicated. The main reasons for this include:[37; 55; 96]

- to assess the thrombotic and haemorrhagic complications, especially in PV and ET
- to monitor the effectiveness and safety of therapy administered, e.g. cytoreductive agent and IFN
- to detect infection early especially those on JAK inhibitor or IFN therapy
- to monitor disease progression, e.g. post-ET or post-PV MF, leukaemic transformation

Serum LDH level is important for monitoring cases of ET, primary and secondary MF. The BSH guidelines advise measuring blood thiamine levels before and throughout fedratinib treatment. Thiamine supplementation should be provided if levels fall below the local normal range to prevent Wernicke's encephalopathy. An iron study should not be overlooked, particularly in the cohort eligible for stem cell transplantation.[55]

- Serum LDH level monitoring is required in ET, PMF and suspected secondary MF.

c. Molecular analysis

Molecular profiling plays an important role in the management of MPN. It assists in:[96; 97]

- prognostication
- risk stratification and guides in allogenic transplant decisions
- identification of subjects suitable for therapeutic modification

d. Radiological

Ultrasound [or computed tomography (CT)/magnetic resonance imaging (MRI)] is an accurate tool for monitoring spleen size and complications (e.g. splenic infarct and thrombosis) in patients with MPN. These imaging studies can also be used to complement the clinical spleen size assessment from a physical examination.

e. Treatment Response

Pharmacological treatment for MPN is continuously evolving and presents inherent challenges. However, it is essential to meticulously monitor these treatments for potential toxicities and development of resistance. Numerous international guidelines and clinical trial protocols offer varying approaches to addressing these issues.

Cytoreductive agents, particularly HU, are frequently used in the treatment of MPN. A change in therapy is warranted when complications arise or when there is evidence of inadequate response or a loss of response. The criteria for intolerance or resistance to HU are outlined in the following table.[96]

Table 8: Definition of resistance/intolerance to hydroxyurea

Myeloproliferative Neoplasm	Definition of Resistance/Intolerance to Hydroxyurea
Polycythaemia vera	1. Need for phlebotomy to keep Hct <45% despite at least three months of treatment at a dose of ≥2 g/day, OR 2. Uncontrolled myeloproliferation (i.e. platelet count >400 x 10^9/L AND WBC count >10 x 10^9/L) despite at least three months of treatment at a dose of ≥2 g/d of treatment, OR 3. Failure to reduce massive* splenomegaly by >50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly despite at least three months of treatment at a dose of ≥2 g/d of treatment, OR 4. Absolute neutrophil count <1.0 x 10^9/L OR platelet count <100 x 10^9/L OR Hb <10 g/dL at the lowest dose required to achieve a complete or partial clinicohaematological response† OR 5. Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities e.g. mucocutaneous manifestations, GI symptoms, pneumonitis or fever at any dose
Essential thrombocythaemia	1. Platelet count >600 x 10^9/L despite a least three months of treatment at a dose of ≥2 g/d of treatment (2.5 g/d in patients with a body weight >80 kg), OR 2. Platelet count >400 x 10^9/L and WBC count <2.5 x 10^9/L at any dose of treatment, OR 3. Platelet count >400 x 10^9/L and Hb <10 g/dL at any dose of treatment, OR 4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of treatment, OR 5. HU-related fever

*Organ extending by >10 cm from the costal margin
†Complete response is defined as Hct <45% without phlebotomy, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, and no disease-related symptoms. Partial response is defined as Hct <45% without phlebotomy or response in ≥3 of other criteria.
Abbreviation: cm = centimetre; g/d = gram per day; g/dL = gram per decilitre; GI = gastrointestinal; Hct = haematocrit; HU = hydroxyurea; kg = kilogram; L = litre; WBC = white blood count

Source: Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: Critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 2011;29:761-770.

7. IMPLEMENTING THE GUIDELINES

Implementation of this CPG is important as it helps provide quality healthcare services based on the best and most recent available evidence, applied to the local scenario and expertise. Various factors and resource implications should be considered for the successful uptake of the CPG recommendations.

7.1. Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:
i) online availability of CPG on multiple websites for healthcare providers
ii) conferences and updates on the management of MPN including those involving professional bodies (e.g. Malaysian Society of Haematology)

Limiting factors in the CPG implementation include:
i) limited awareness and knowledge in the management of MPN among healthcare providers
ii) different levels of expertise and wide variation in practice due to resource constraints

7.2. Potential Resource Implications

Many clinicians in Malaysia are unfamiliar with the MPN spectrum as many patients either go undiagnosed in the rural areas or are put under the sole care of the haematologist. The general physician or family medicine specialist (FMS) may also inadvertently order many inappropriate investigations without following a streamlined thought process in approaching a suspected MPN (e.g. unnecessary *JAK2* testing for transient and/or secondary causes of polycythaemia or thrombocytosis). It causes needless financial strain on the healthcare system.

In addition, novel therapy in the treatment paradigm of MPN patients who fail first-line therapy is restricted by the high costs of JAK inhibitors within the limited healthcare budget. Although a cure can be obtained by stem-cell transplant for high-risk MPNs like MF, it is limited by factors e.g. expertise, facilities and patients' acceptance in performing such a procedure nationwide. Since MPN is a chronic disease, patients will need lifelong treatment and therefore impose significant costs on the healthcare system.

In line with the key recommendations in this CPG, the following are proposed as clinical audit indicators for the quality management of MPN:

$$\text{Percentage of newly diagnosed MF patients who undergo risk stratification prior to initiation of treatment} = \frac{\text{Number of newly diagnosed MF patients who had risk stratification prior to initiation of treatment within the audit period}}{\text{Total number of newly diagnosed MF patients within the same audit period}} \times 100\%$$

*Target of 70%

$$\text{Percentage of newly diagnosed high-risk PV patients in primary care who were started on aspirin} = \frac{\text{Number of newly diagnosed high-risk PV in patients primary care started on aspirin within the audit period}}{\text{Total number of newly diagnosed high-risk PV patients in primary care within the same audit period}} \times 100\%$$

*Target of 70%

Implementation strategies will be developed following the approval of the CPG by MoH which include the Quick Reference and Training Module and they are available in the MoH and Academy of Medicine of Malaysia (AMM) websites after development.

REFERENCES

1. World Health Organization Classification of Tumours Editorial Board. Haematolymphoid Tumours. 5th ed. Geneva: World Health Organization; 2022.
2. Harrison C, Sekhar M, Mitchell C, et al. Pan-London Haemato-Oncology Clinical Guidelines Acute Leukaemias and Myeloid Neoplasms Part 4: Myeloproliferative Neoplasms. London: RM Partners, South East London Cancer Alliance, North Central and East London Cancer Alliance; 2020.
3. Srour SA, Devesa SS, Morton LM, et al. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-12. Br J Haematol. 2016;174(3):382-396.
4. Yap YY, Law KB, Sathar J, et al. The epidemiology and clinical characteristics of myeloproliferative neoplasms in Malaysia. Exp Hematol Oncol. 2018;7:31.
5. Barbui T, Ghirardi A, Carobbio A, et al. Thrombosis in myeloproliferative neoplasms: a viewpoint on its impact on myelofibrosis, mortality, and solid tumors. Blood Cancer J. 2024;14(1):188.
6. Ministry of Health Malaysia. Diagnosis and Management of Myeloproliferative Disorders. Kuala Lumpur: Ministry of Health Malaysia; 2004.
7. Cerquozzi S, Tefferi A. Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J. 2015;5(11):e366.
8. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leuk. 2013;27(9):1874-1881.
9. Szuber N, Mudireddy M, Nicolosi M, et al. 3023 Mayo Clinic Patients With Myeloproliferative Neoplasms: Risk-Stratified Comparison of Survival and Outcomes Data Among Disease Subgroups. Mayo Clin Proc. 2019;94(4):599-610.
10. Finazzi G, Carobbio A, Thiele J, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. Leuk. 2012;26(4):716-719.
11. Gisslinger H, Jeryczynski G, Gisslinger B, et al. Clinical impact of bone marrow morphology for the diagnosis of essential thrombocythemia: comparison between the BCSH and the WHO criteria. Leuk. 2015;30(5):1126-1132.
12. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. J Clin Oncol. 2011;29(23):3179-3184.
13. Guglielmelli P, Pacilli A, Rotunno G, et al. Presentation and outcome of patients with 2016 WHO diagnosis of prefibrotic and overt primary myelofibrosis. Blood. 2017;129(24):3227-3236.
14. Silver RT, Krichevsky S. Distinguishing essential thrombocythemia JAK2V617F from polycythemia vera: limitations of erythrocyte values. Haematologica. 2019;104(11):2200-2205.
15. Loscocco GG, Guglielmelli P, Gangat N, et al. Clinical and molecular predictors of fibrotic progression in essential thrombocythemia: A multicenter study involving 1607 patients. Am J Hematol. 2021;96(11):1472-1480.
16. Shah S, Mudireddy M, Hanson CA, et al. Marked elevation of serum lactate dehydrogenase in primary myelofibrosis: clinical and prognostic correlates. Blood Cancer J. 2017;7(12):657.
17. Mudireddy M, Barraco D, Hanson CA, et al. The prognostic relevance of serum lactate dehydrogenase and mild bone marrow reticulin fibrosis in essential thrombocythemia. Am J Hematol. 2017;92(5):454-459.

18. Beer PA, Campbell PJ, Green AR. Comparison of different criteria for the diagnosis of primary myelofibrosis reveals limited clinical utility for measurement of serum lactate dehydrogenase. Haematologica. 2010;95(11):1960-1963.
19. Lupak O, Han X, Xie P, et al. The role of a low erythropoietin level for the polycythemia vera diagnosis. Blood Cells Mol Dis. 2020;80:102355.
20. Saki N, Shirzad R, Rahim F, et al. Estimation of diagnosis and prognosis in ET by assessment of CALR and JAK2(V617F) mutations and laboratory findings: a meta-analysis. Clin Transl Oncol. 2017;19(7):874-883.
21. Kong H, Liu Y, Luo S, et al. Frequency of Calreticulin (CALR) Mutation and Its Clinical Prognostic Significance in Essential Thrombocythemia and Primary Myelofibrosis: A Meta-analysis. Intern Med. 2016;55(15):1977-1984.
22. Tefferi A, Lasho TL, Finke CM, et al. Targeted deep sequencing in primary myelofibrosis. Blood Adv. 2016;1(2):105-111.
23. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390.
24. Mejia-Ochoa M, Acevedo Toro PA, Cardona-Arias JA. Systematization of analytical studies of polycythemia vera, essential thrombocythemia and primary myelofibrosis, and a meta-analysis of the frequency of JAK2, CALR and MPL mutations: 2000-2018. BMC Cancer. 2019;19(1):590.
25. Lussana F, Caberlon S, Pagani C, et al. Association of V617F Jak2 mutation with the risk of thrombosis among patients with essential thrombocythaemia or idiopathic myelofibrosis: a systematic review. Thromb Res. 2009;124(4):409-417.
26. Chin-Yee B, Bhai P, Cheong I, et al. A Rational Approach to JAK2 Mutation Testing in Patients with Elevated Hemoglobin: Results from the JAK2 Prediction Cohort (JAKPOT) Study. J Gen Intern Med. 2022;38(8):1828-1833.
27. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024;99(4):697-718.
28. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(5):801-821.
29. Tefferi A, Nicolosi M, Mudireddy M, et al. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patients. Leukemia. 2018;32(5):1189-1199.
30. Tang G, Hidalgo Lopez JE, Wang SA, et al. Characteristics and clinical significance of cytogenetic abnormalities in polycythemia vera. Haematologica. 2017;102(9):1511-1518.
31. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood. 2011;118(2):401-408.
32. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol. 2012;30(33):4098-4103.
33. Kim SY, Bae SH, Bang SM, et al. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. Korean J Intern Med. 2021;36(1):45-62.
34. Yang E, Wang M, Wang Z, et al. Comparison of the effects between MPL and JAK2V617F on thrombosis and peripheral blood cell counts in patients with essential thrombocythemia: a meta-analysis. Ann Hematol. 2021;100(11):2699-2706.
35. Stuckey R, Ianotto JC, Santoro M, et al. Validation of thrombotic risk factors in 1381 patients with essential thrombocythaemia: A multicentre retrospective real-life study. Br J Haematol. 2022;199(1):86-94.

36. Gerds AT, Gotlib J, Ali H, et al. Myeloproliferative Neoplasms, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(9):1033-1062.
37. Vannucchi AM, Barbui T, Cervantes F, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v85-99.
38. McMullin MFF, Mead AJ, Ali S, et al. A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis: A British Society for Haematology Guideline. Br J Haematol. 2019;184(2):161-175.
39. Bhatia S, Kaur P, Kaur G, et al. Revisiting the impact of serial therapeutic phlebotomy in polycythaemia on laboratory and clinical parameters using a fixed interval and fixed volume protocol. Transfus Clin Biol. 2023;30(1):63-68.
40. Parra Salinas I, Recasens Flores V, Montañés M, et al. Therapeutic erythroapheresis: Experience in patients with polycythemia vera and secondary erythrocytosis. Med Clin (Barc). 2020;154(1):16-19.
41. Nguyen TH, Bach KQ, Vu HQ, et al. Therapeutic thrombocytapheresis in myeloproliferative neoplasms: A single-institution experience. J Clin Apher. 2021;36(1):101-108.
42. Polverelli N, Hernández-Boluda JC, Czerw T, et al. Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: a Position Paper on behalf of the Chronic Malignancies Working Party of the EBMT. Lancet Haematol. 2023;10(1):e59-e70.
43. Polverelli N, Mauff K, Kroger N, et al. Impact of spleen size and splenectomy on outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis: A retrospective analysis by the chronic malignancies working party on behalf of European society for blood and marrow transplantation (EBMT). Am J Hematol. 2021;96(1):69-79.
44. Ponce SB, Chhabra S, Hari P, et al. Pretransplant Splenic Irradiation in Patients With Myeloproliferative Neoplasms. Adv Radiat Oncol. 2022;7(5):100964.
45. Squizzato A, Romualdi E, Passamonti F, et al. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. Cochrane Database Syst Rev. 2013;2013(4):CD006503.
46. Chu DK, Hillis CM, Leong DP, et al. Benefits and Risks of Antithrombotic Therapy in Essential Thrombocythemia: A Systematic Review. Ann Intern Med. 2017;167(3):170-180.
47. McMullin MF, Harrison CN, Ali S, et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol. 2019;184(2):176-191.
48. Huenerbein K, Sadjadian P, Becker T, et al. Direct oral anticoagulants (DOAC) for prevention of recurrent arterial or venous thromboembolic events (ATE/VTE) in myeloproliferative neoplasms. Ann Hematol. 2021;100(8):2015-2022.
49. Barbui T, De Stefano V, Carobbio A, et al. Direct oral anticoagulants for myeloproliferative neoplasms: results from an international study on 442 patients. Leuk. 2021;35(10):2989-2993.
50. Baysal M, Bayrak M, Eskazan AE. Current evidence on the use of direct oral anticoagulants in patients with myeloproliferative neoplasm: a systematic review. Expert Rev Hematol. 2023;16(2):131-140.
51. Hamulyak EN, Daams JG, Leebeek FWG, et al. A systematic review of antithrombotic treatment of venous thromboembolism in patients with myeloproliferative neoplasms. Blood Adv. 2021;5(1):113-121.
52. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(9):1465-1487.
53. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013;368(1):22-33.

54. Samuelson B, Chai-Adisaksopha C, Garcia D. Anagrelide compared with hydroxyurea in essential thrombocythemia: a meta-analysis. J Thromb Thrombolysis. 2016;40(4):474-479.
55. McLornan DP, Psaila B, Ewing J, et al. The management of myelofibrosis: A British Society for Haematology Guideline. Br J Haematol. 2024;204(1):136-150.
56. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019;134(18):1498-1509.
57. Mascarenhas J, Kosiorek HE, Prchal JT, et al. A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. Blood. 2022;139(19):2931-2941.
58. Bewersdorf JP, Giri S, Wang R, et al. Interferon Therapy in Myelofibrosis: Systematic Review and Meta-analysis. Clin Lymphoma Myeloma Leuk. 2020;20(10):e712-e723.
59. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020;7(3):e196-e208.
60. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-435.
61. Masciulli A, Ferrari A, Carobbio A, et al. Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis. Blood Adv. 2020;4(2):380-386.
62. Lussana F, Cattaneo M, Rambaldi A, et al. Ruxolitinib-associated infections: A systematic review and meta-analysis. Am J Hematol. 2018;93(3):339-347.
63. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial. J Clin Oncol. 2023;41(19):3534-3544.
64. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. Blood. 2017;130(17):1889-1897.
65. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
66. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366(9):787-798.
67. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. Lancet Haematol. 2017;4(5):e225-e236.
68. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2018;4(5):652-659.
69. Mesa RA, Kiladjian JJ, Catalano JV, et al. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients With Myelofibrosis. J Clin Oncol. 2017;35(34):3844-3850.
70. Harrison CN, Vannucchi AM, Platzbecker U, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol. 2017;5(2):e73-e81.
71. Verstovsek S, Gerds AT, Vannucchi AM, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. Lancet. 2023;401(10373):269-280.

72. Pardanani A, Harrison C, Cortes JE, et al. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015;1(5):643-651.
73. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020;95(6):594-603.
74. Gotic M, Egyed M, Gercheva L, et al. Cardiovascular Safety of Anagrelide Hydrochloride versus Hydroxyurea in Essential Thrombocythaemia. Cardiovasc Toxicol. 2021;21(3):236-247.
75. Kanakura Y, Miyakawa Y, Wilde P, et al. Phase III, single-arm study investigating the efficacy, safety, and tolerability of anagrelide as a second-line treatment in high-risk Japanese patients with essential thrombocythemia. Int J Hematol. 2014;100(4):353-360.
76. Kanakura Y, Shirasugi Y, Yamaguchi H, et al. A phase 3b, multicenter, open-label extension study of the long-term safety of anagrelide in Japanese adults with essential thrombocythemia. Int J Hematol. 2018;108(5):491-498.
77. Schuermans C, Mazure D, Van Eygen K, et al. Management of polycythemia vera: Recommendations from the BHS MPN subcommittee anno 2021. Belg J Hematol. 2021;12(6):258-274.
78. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(12):1599-1613.
79. Howell C, Douglas K, Cho G, et al. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. British Committee for Standards in Haematology. Transfus Med. 2015;25(2):57-78.
80. Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020;26(7):1247-1256.
81. Hernandez-Boluda JC, Pereira A, Kroger N, et al. Determinants of survival in myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation. Leuk. 2021;35(1):215-224.
82. Kroger N, Sbianchi G, Sirait T, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. Leuk. 2021;35(12):3551-3560.
83. Robin M, Porcher R, Orvain C, et al. Ruxolitinib before allogeneic hematopoietic transplantation in patients with myelofibrosis on behalf SFGM-TC and FIM groups. Bone Marrow Transplant. 2021;56(8):1888-1899.
84. Tamari R, McLornan DP, Ahn KW, et al. A simple prognostic system in patients with myelofibrosis undergoing allogeneic stem cell transplantation: a CIBMTR/EBMT analysis. Blood Adv. 2023;7(15):3993-4002.
85. Landtblom AR, Andersson TM, Johansson ALV, et al. Pregnancy and childbirth outcomes in women with myeloproliferative neoplasms-a nationwide population-based study of 342 pregnancies in Sweden. Leuk. 2022;36(10):2461-2467.
86. Ministry of Health Malaysia. Training Manual on Management of Post Partum Haemorrhage (PPH) 2016. Putrajaya: Ministry of Health Malaysia; 2016.
87. Maze D, Kazi S, Gupta V, et al. Association of Treatments for Myeloproliferative Neoplasms During Pregnancy With Birth Rates and Maternal Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(10):e1912666.
88. Wille K, Bernhardt J, Sadjadian P, et al. The management, outcome, and postpartum disease course of 41 pregnancies in 20 women with polycythemia vera. Eur J Haematol. 2021;107(1):122-128.

89. Skeith L, Carrier M, Robinson SE, et al. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. Blood. 2017;129(8):934-939.
90. Schrickel L, Heidel FH, Sadjadian P, et al. Interferon alpha for essential thrombocythemia during 34 high-risk pregnancies: outcome and safety. J Cancer Res Clin Oncol. 2020;147(5):1481-1491.
91. Podoltsev NA, Wang X, Wang R, et al. Diet and Risk of Myeloproliferative Neoplasms in Older Individuals from the NIH-AARP Cohort. Cancer Epidemiol Biomarkers Prev. 2020;29(11):2343-2350.
92. Mendez Luque LF, Avelar-Barragan J, Nguyen H, et al. The NUTRIENT Trial (NUTRitional Intervention among myEloproliferative Neoplasms): Results from a Randomized Phase I Pilot Study for Feasibility and Adherence. Cancer Res Commun. 2024;4(3):660-670.
93. Gowin K, Langlais BT, Kosiorek HE, et al. The SIMM study: Survey of integrative medicine in myeloproliferative neoplasms. Cancer Med. 2020;9(24):9445-9453.
94. Huberty J, Eckert R, Dueck A, et al. Online yoga in myeloproliferative neoplasm patients: results of a randomized pilot trial to inform future research. BMC Complement Altern Med. 2019;19(1):121.
95. Nee A, Clifford R. University Hospital Limerick GP referral Guide for Haematology. Limerick: University Hospital Limerick; 2023.
96. Gerds AT, Gotlib J, Abdelmessieh P, et al. Myeloproliferative Neoplasms Version 2.2024. Pennsylvania: National Comprehensive Cancer Network (NCCN); 2024.
97. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leuk. 2018;32(5):1057-1069.

Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective pharmacological treatments in MPN?

1. MYELOPROLIFERATIVE DISORDERS/
2. (myeloproliferative adj1 disorder*).tw.
3. PRIMARY MYELOFIBROSIS/
4. (agnogenic adj2 myeloid metaplasia*).tw.
5. (bone marrow adj2 fibros#s).tw.
6. chronic idiopathic myelofibrosis.tw.
7. ((idiopathic or primary) adj1 myelofibros#s).tw.
8. (myeloid adj1 metaplasia*).tw.
9. myelofibros#s.tw.
10. myeloscleros#s.tw.
11. (nonleuk?emic adj1 myelos#s).tw.
12. THROMBOCYTHEMIA, ESSENTIAL
13. ((essential or primary or h?emorrhagic or idiopathic) adj1 thrombocyth?emia*).tw.
14. (primary adj1 thrombocytos#s).tw.
15. POLYCYTHEMIA VERA
16. (primary adj1 polycyth?emia*).tw.
17. (polycyth?emia adj2 rubra vera*).tw.
18. polycyth?emia vera*.tw.
19. ((post-essential thrombocyth?emia or post ET) adj2 myelofibrosis).tw
20. (post-ET adj1 myelofibrosis).tw.
21. ((post-polycyth?emia vera or post PV) adj2 myelofibrosis).tw.
22. (post-PV adj1 myelofibrosis).tw.
23. HYDROXYUREA/
24. hydroxycarbamid*.tw.
25. hydroxyurea.tw.
26. ((pegylated or peg) adj1 interferon*).tw.
27. pegylated-interferon.tw.
28. peg-interferon.tw.
29. INTERFERONS/
30. interferon*.tw.
31. PLATELET AGGREGATION INHIBITORS/
32. ((antiplatelet or anti-platelet) adj1 (agent* or drug*)).tw.
33. (platelet aggregation adj2 inhibitor*).tw.

34. (blood platelet adj2 (antagonist* or antiaggregant*)).tw.
35. (platelet adj1 (antagonist* or inhibitor* or antiaggregant*)).tw.
36. blood platelet aggregation adj3 inhibitor*).tw.
37. ANTICOAGULANTS/
38. ((anticoagula* or anti-coagula*) adj1 (agent* or drug*)).tw.
39. anticoagulant*.tw.
40. anti-coagulant*.tw.
41. (indirect adj2 thrombin inhibitor*).tw.
42. FACTOR XA INHIBITORS/
43. (direct-acting adj2 oral anticoagulant*).tw.
44. direct acting adj3 oral anticoagulant*).tw.
45. direct adj3 factor xa inhibitor*).tw.
46. factor xa adj2 inhibitor*).tw.
47. JANUS KINASE INHIBITORS/
48. jak adj1 inhibitor*).tw.
49. (janus kinase adj2 inhibitor*).tw.
50. ruxolitinib*.tw.
51. BUSULFAN/
52. busulfan.tw.
53. busulphan.tw.
54. busulfex.tw.
55. anagrelide.tw.
56. ERYTHROPOIETIN/
57. erythropoietin.tw.
58. DARBEPOETIN ALFA/
59. darbepo?etin alfa.tw.
60. DANAZOL/
61. danazol.tw.
62. THALIDOMIDE/
63. thalidomide.tw.
64. thalomid.tw.
65. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
66. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
67. 65 and 66
68. limit 67 to (english language and humans and yr=”2004 -Current”)

Appendix 2

CLINICAL QUESTIONS

Diagnosis and Investigation

*Clinical features and common complications of each subtype in MPN -
- PV
- ET
- PMF
- Post-PV MF
- Post-ET MF

*WHO diagnostic criteria for each subtype in MPN -
- PV
- ET
- PMF
  - Early fibrosis
  - Overt fibrosis
- Post-PV MF
- Post-ET MF

*Specific complications of MPN -
- Acquired von Willebrand disease (VWD)
- Blast transformation
- Portal hypertension

▪ What are the accurate investigations to diagnose MPN?
- Full blood count
- Lactate dehydrogenase
- Serum erythropoietin
- Morphology
  - Full blood picture
  - Bone marrow aspiration
  - Bone marrow biopsy
- Cytogenetic
  - Karyotyping
- Molecular analysis
  - *BCR::ABL1*
  - *JAK2 p.V617F*
  - *JAK2* exon 12 mutations
  - *CALR* mutations
  - *MPL* mutations

Treatment

1. What are the risk stratification criteria (including new mutation profile and thrombosis risk) for each subtype of MPN?
   - PV
   - ET
   - PMF
   - Post-PV MF
   - Post-ET MF

2. What are the accurate assessment tools to assess burden of symptoms in MPN?
   - Myeloproliferative Neoplasms Symptoms Assessment Form (MPN-SAF)
   - MPN-SAF Total Symptom Score (TSS)
3. What are the safe and effective non-pharmacological treatments in MPN?
   - Phlebotomy
   - Plateletpheresis
   - Transfusion support
   - Splenectomy
   - Splenic irradiation
4. What are the safe and effective pharmacological treatments in MPN?
   - PV
     - Standard therapy - hydroxyurea, pegylated (PEG)-interferon/ interferon, anti-platelet and anticoagulant, ruxolitinib, busulfan
     - Drug in development/Novel therapy
   - ET
     - Standard therapy - hydroxyurea, PEG-interferon/interferon, anti-platelet and anticoagulant, anagrelide, busulfan
     - Drug in development/Novel therapy
   - PMF
     - Standard therapy - hydroxyurea, anti-platelet and anticoagulant, ruxolitinib, erythropoietin, darbepoetin, danazol, thalidomide, busulfan
     - Drug in development/Novel therapy
   - Post-PV MF
     - Standard therapy - hydroxyurea, anti-platelet and anticoagulant, ruxolitinib, erythropoietin, darbepoetin, danazol, thalidomide, busulfan
     - Drug in development/Novel therapy
   - Post-ET MF
     - Standard therapy - hydroxyurea, anti-platelet and anticoagulant, ruxolitinib, erythropoietin, darbepoetin, danazol, thalidomide, busulfan
     - Drug in development/Novel therapy
5. What are the safe and effective treatments for emergency cytoreduction in MPN?
   - Acute coronary syndrome
   - Acute cerebrovascular accident/Stroke
6. What are the indications, effectiveness and safety for stem-cell transplant in MPN?
7. Is nutritional/supplementation support effective and safe in MPN?

Pregnancy

1. What are the safe and effective treatments for pregnant women with MPN?

Referral and Follow-up

- What are the referral criteria of MPN to the haematologist?
- What are the monitoring parameters (including investigation) in MPN?

MEDICATION TABLE FOR MYELOPROLIFERATIVE NEOPLASMS

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
Anticoagulant			
LMWH Enoxaparin	**Pulmonary embolism** SC 1 mg/kg BD **Venous thromboembolism; Prophylaxis** (<100 kg): SC 40 mg BD; adjust after 3 - 4 doses of the initial dosage (≥100 kg): SC 0.5 mg/kg BD based on actual body weight **Renal impairment** (CrCl 20 - 30 mL/min): prophylaxis SC 20 - 40 mg OD, treatment SC 1 mg/kg OD or consider unfractionated heparin (CrCl <20 mL/min or renal replacement therapy): Avoid use unless anti-factor Xa levels monitoring is available **Hepatic impairment:** Effect unknown; studies have not been conducted **Low-weight patients** (e.g. women <45 kg or men <57 kg): Observe frequently for signs and symptoms of bleeding. Unfractionated heparin may be more appropriate for patients weighing <40 kg **Obesity (in thromboprophylaxis):** (anti-factor Xa levels monitoring is recommended) <50 kg : 20 mg OD 131 - 170 kg: 80 mg OD 50 - 90 kg : 40 mg OD >170 kg : 0.6 mg/kg/day 91 - 130 kg: 60 mg OD	Gastrointestinal: Diarrhoea, Nausea Hematologic: Anaemia, Haemorrhage, Thrombocytopenia Hepatic: Raised liver enzymes level Other: Fever	**Pregnancy:** Foetal harm risk cannot be ruled out **Lactation:** Infant risk cannot be ruled out **Contraindications:** • Active major bleeding • History of immune-mediated heparin-induced thrombocytopenia within the past 100 days or in presence of circulating antibodies • Hypersensitivity to benzyl alcohol (present in multi-dose formulation) • Hypersensitivity to enoxaparin sodium, heparin or pork products **Boxed warning:** Epidural or spinal haematomas which may result in long-term or permanent paralysis.
Direct Thrombin Inhibitor			
Dabigatran	**Venous thromboembolism** Secondary prophylaxis following initial therapy: 150 mg BD PO Treatment following parenteral therapy: 150 mg BD PO after 5 - 10 days of parenteral anticoagulation	Gastrointestinal: Oesophagitis, Gastritis, Gastroesophageal reflux disease, Gastrointestinal haemorrhage,	**Pregnancy:** Foetal harm has been demonstrated, not recommended

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	Renal impairment (CrCl 30 - 50 mL/min) with concomitant P-glycoprotein inhibitor: Avoid use (CrCl <30 mL/min or dialysis): Contraindicated (Acute renal failure developing during therapy): Discontinue and consider an alternate anticoagulant **Hepatic impairment** [moderate hepatic impairment (Child-Pugh B)]: Large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics	Gastrointestinal ulcer, Indigestion Haematologic: Haemorrhage	**Lactation:** Infant risk cannot be ruled out **Contraindications:** • Active pathological bleeding • Mechanical prosthetic heart valve • Serious hypersensitivity to dabigatran or any excipient of the product **Boxed warning:** Premature discontinuation increases the risk of thrombotic events
Platelet Aggregation Inhibitor / Blood Modifier Agent			
Aspirin Aspirin/Glycine	75 - 100 mg OD PO Enteric-coated tablets: may be taken without food Extended-release capsules: Do not take 2 hours before or 1 hour after consuming alcohol **Renal Impairment** (CrCl <10 mL/min): Avoid use (CAPD): Avoid use if possible, but if use is necessary, begin with low doses (CRRT): No dosage adjustment (Haemodialysis): administer after haemodialysis on dialysis days **Hepatic impairment** (severe, Child Pugh score ≥9): Avoid use	Gastric ulcer Haemorrhage, Exudative age-related macular degeneration	**Pregnancy**: Foetal harm is similar to normal population. There is only low risk of postpartum hemorrhage for low dose aspirin. **Lactation**: Infant risk cannot be ruled out. Discontinue treatment with aspirin or discontinue breastfeeding (risk of Reye's syndrome) Oral extended release forms are contraindicated if patient has hypersensitivity to NSAIDs

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
Platelet reducing agent / Blood Modifier Agent			
Anagrelide	Initial, 0.5 mg BD - QID PO or 1 mg BD PO for at least 1 week; titrate to the lowest effective dose; do not exceed 0.5 mg/day dose increase in any 1 week; maximum 2.5 mg/dose and 10 mg/day **Hepatic impairment** (moderate, Child Pugh score 7 - 9): Begin with 0.5 mg OD PO for at least 1 week, and if tolerated, may consider dosage increase; do not increase dose more than 0.5 mg/day in any 1 week (severe, Child Pugh score ≥9): Avoid use	Cardiovascular: Oedema, palpitations Gastrointestinal: Abdominal pain, diarrhoea, nausea Nervous system: Headache, dizziness, pain Neuromuscular & skeletal: Asthenia Respiratory: Dyspnoea	**Pregnancy**: Foetal risk cannot be ruled out, not recommended **Lactation**: Infant risk cannot be ruled out. Breastfeeding is not recommended during anagrelide therapy and for 1 week after the last dose due to the risk of serious AEs, including thrombocytopenia to the infant
Immunomodulators			
Peginterferon Alpha-2a	**Essential Thrombocythemia** Initial, SC 90 mcg/week, modify dose based on efficacy and toxicity **Polycythemia vera** Initial, SC 90 mcg/week, escalated every 2 weeks to 135 mcg/week (maximum 180 mcg/week) **Renal Impairment:** CrCl <30 mL/min or ESKD requiring haemodialysis: Reduce to SC 135 mcg/week; if severe AEs develop, reduce to SC 90 mcg/week; if intolerance persists, discontinue therapy. **Hepatic impairment** Monitor liver function ALT ≥10x ULN: Consider discontinuation of therapy	Dermatologic: Alopecia, pruritus Gastrointestinal: Abdominal pain, anorexia, diarrhoea, nausea, vomiting Hematologic: Neutropenia Hepatic: Raised liver enzymes level Nervous system: Anxiety,	**Pregnancy:** Should be used with cautious under expert's supervision **Lactation:** Infant risk cannot be ruled out, relatively contraindicated, should be used with cautious under expert's supervision **Contraindications:** • Autoimmune hepatitis • Hepatic decompensation (Child-Pugh class B and C) in cirrhotic before or during treatment

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	ALT ≥5x ULN: Consider reducing dose to SC 135 mcg/week or discontinue temporarily **Depression** Moderate: Reduce to SC 90 - 135 mcg/week; if symptoms improve and are stable for 4 weeks, may increase to normal dose Severe: Discontinue therapy permanently and obtain immediate psychiatric consultation **Neutropenia** ANC 0.5 - 0.75 x 10^9/L: Decrease to SC 135 mcg/week ANC <0.5 x 10^9/L: Delay until ANC is >0.5 x 10^9/L, then restart at SC 90 mcg/week **Thrombocytopenia** Platelet 25 - 50 x 10^9/L: Decrease to SC 90 mcg/week Platelet <25 x 10^9/L: Discontinue therapy	depression, dizziness, fatigue, headache, insomnia, irritability, rigors Neuromuscular & skeletal: Arthralgia, myalgia Respiratory: Cough, flu-like symptoms Miscellaneous: Fever	• Known hypersensitivity to IFN-alfa or its components **Boxed warning:** May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischaemic and infectious disorders
Ropeginterferon Alfa-2b-njft	**Polycythemia vera** HU-naïve: Initial, SC 100 mcg every 2 weeks; increase by SC 50 mcg every 2 weeks (maximum 500 mcg every 2 weeks) until the haematological parameters are stabilised (Hct <45%, platelets <400 x 10^9/L and WBC <10 x 10^9/L). Transitioning from HU: Initial, SC 50 mcg every 2 weeks in combination with HU; reduce the total biweekly HU dose by 20% to 40% every 2 weeks during weeks 3 through week 12 and discontinue by week 13. Increase ropeginterferon alfa-2b-njft by SC 50 mcg every 2 weeks (maximum 500 mcg every 2 weeks) until the haematological parameters are stabilized (Hct <45%, platelets <400 x 10^9/L and WBC <10 x 10^9/L). Maintain the 2-week dosing interval at which haematological stability is achieved for at least 1 year; after haematological stability for at least 1	Cardiovascular: Oedema, hypertension Dermatologic: Alopecia, hyperhidrosis, pruritus, skin rash Gastrointestinal: Abdominal pain, decreased appetite, diarrhoea, nausea Haematologic: Leucopenia, neutropenia, thrombocytopenia	**Pregnancy:** May cause foetal harm, not recommended **Lactation:** Infant risk cannot be ruled out, not recommended **Contraindications:** • Autoimmune disease • Transplantation and receiving immunosuppressants • Known hypersensitivity to IFN-alfa or its components • Psychiatric disorders

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	year on a stable dose, the dosing interval may be expanded to every 4 weeks. **Renal impairment** eGFR <30 mL/min: Avoid use **Hepatic impairment** Child-Pugh B or C: contraindicated Liver enzyme elevation above baseline with concomitant bilirubin elevation or other evidence of hepatic decompensation: Interrupt treatment until recovery, restart at dose 50 mcg lower than the interrupted dose. Severe or unstable cardiovascular disease: Avoid use Colitis signs or symptoms: Discontinue treatment **Cytopenia** Hb <8 g/dL or platelets 25 - 50 x 10^9/L or WBC 1 - 2 x 10^9/L: Decrease dose by 50 mcg every 2 weeks intervals until Hb >10 g/dL or platelets >75 x 10^9/L or WBC >3 x 10^9/L Hb life threatening or requires urgent intervention or platelets <25 x 10^9/L or WBC <1 x 10^9/L: Interrupt treatment until Hb >10 g/dL or platelets >75 x 10^9/L or WBC >3 x 10^9/L **Depression** Mild, without suicidal ideation: Consider psychiatric consultation if lasts >8 weeks Moderate, without suicidal ideation: Consider dose reduction and psychiatric consultation	Hepatic: Raised liver enzymes level, infection Nervous system: Depression, dizziness, fatigue, headache, sleep disorder, vertigo Neuromuscular & skeletal: Arthralgia, muscle spasm, musculoskeletal pain, myalgia Ophthalmic: Eye disease Respiratory: Flu-like symptoms, nasopharyngitis, upper respiratory tract infection	**Boxed warning:** May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischaemic and infectious disorders Live vaccine: increased risk of infection CNS depressants: increased risk of sedation

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	Severe, or any severity with suicidal ideation: Discontinue therapy and recommend psychiatric consultation **Dermatologic toxicity,** clinically significant: Consider discontinuation **Endocrine disorders** that cannot be adequately managed: Discontinue treatment **Hyperlipidaemia** (triglyceride elevation persistent, markedly elevated): Consider discontinuation **Ophthalmologic toxicity** (new or worsening eye disorders): Discontinue treatment **Pancreatitis** Possible: Interrupt treatment and evaluate Confirmed: Consider discontinuation **Pulmonary infiltrates or pulmonary function impairmen**t: Discontinue treatment		
Antineoplastic Agent			
Hydroxyurea	20 - 30 mg/kg OD PO Do not open capsules and avoid exposure to crushed or opened capsules. Take at the same time each day, with a glass of water. **Renal Impairment:** CrCl <60 mL/min or ESKD: Give 25 - 50% of the dose Haemodialysis: Give 25 - 50% of the dose, given after haemodialysis **Pulmonary toxicity:** Discontinue and manage with corticosteroids	Alopecia, Rash, Nail discolouration, Skin or oral ulcer, Dry skin, Diarrhoea, Nausea, Cytopaenia, Infection, Arthralgia, Backache, Headache, Dizziness, Cough, Dyspnoea, Fatigue, Fever	HU is carcinogenic. **Pregnancy**: May cause foetal harm **Lactation**: Advise women not to breastfeed during HU therapy due to the potential risk for serious AEs Live vaccines: increased risk of infection

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
Busulfan	2 - 4 mg/day PO and to withhold once platelets <200 x 10^9/L or WBC <3 x 10^9/L **Hepatic impairment** Severe: Not recommended. **Myelosuppression**: Reduce dose or discontinue at first sign of depressed bone marrow function	Endocrine metabolic: Hyperglycaemia, Hypokalaemia, Hypomagnaesemia Gastrointestinal: Abdominal pain, Diarrhoea, Loss of appetite, Nausea, Stomatitis, Vomiting Neurologic: Headache, Insomnia Psychiatric: Anxiety Other: Fever	Busulfan is carcinogenic. **Pregnancy**: Foetal harm has been demonstrated **Lactation**: Infant risk cannot be ruled out
Tyrosine Kinase Inhibitor (JAK inhibitor)			
Ruxolitinib	**Myelofibrosis, intermediate- or high-risk** Baseline platelet >200 x 10^9/L: 20 mg BD PO Baseline platelet 101 - 200 x 10^9/L: 15 mg BD PO Baseline platelet 50 - 100 x 10^9/L: 5 mg BD PO **Polycythemia vera, intolerant to hydroxyurea:** 10 mg BD PO **Renal Impairment** CrCl 15 - 59 mL/min: **Myelofibrosis:** • Platelet 100 - 150 x 10^9/L: 10 mg BD PO • Platelet 50 - 100 x 10^9/L: 5 mg OD PO • Platelet <50 x 10^9/L: Avoid **Polycythaemia vera**: 5 mg BD PO CrCl <15 mL/min, not on dialysis: Avoid use	Cytopaenias, Bruising, Dizziness, Headache, Urinary tract infection, Raised liver enzymes level, Hypercholesterolaemia	**Pregnancy:** Not recommended **Lactation:** Discontinue breastfeeding during treatment until 2 weeks after the final dose

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	CVVHD: 5 mg every other day to OD PO **Hepatic Impairment** : Child-Pugh A, B or C **Myelofibrosis:** • Platelet 100 - 150 x 10^9/L: 10 mg BD PO • Platelet 50 - 100 x 10^9/L: 5 mg OD PO • Platelet <50 x 10^9/L: Avoid **Polycythaemia vera**: 5 mg BD PO **Thrombocytopenia / Myelosuppression:** Platelet <25 x 10^9/L or ANC <0.5 x 10^9/L after the initiation: Interrupt dose For other situation: refer to **Table 8 on Ruxolitinib specific dose adjustment**		
Momelotinib	**Myelofibrosis, intermediate or high-risk, primary or secondary, with anaemia:** 200 mg OD PO **Hepatic impairment** Severe, Child-Pugh C: Initial dose, 150 mg OD PO **Hepatotoxicity** AST and/or ALT ≥5x ULN (or ≥5x baseline, if baseline is abnormal) and/or total bilirubin ≥2x ULN (or ≥2x baseline, if baseline is abnormal): Interrupt treatment **Other non-haematologic adverse event (Grade 3 or higher)**: Interrupt treatment until toxicity resolves to Grade 1 or lower or baseline **Neutropenia (ANC <0.5 x 10^9/L):** Interrupt treatment until ANC ≥0.75 x 10^9/L	Dermatologic: Rash Gastrointestinal: Diarrhoea, Nausea Hematologic: Haemorrhage, Thrombocytopenia Hepatic: Raised liver enzymes level Neurologic: Dizziness Other: Bacterial infection, Fatigue, Fever	**Pregnancy:** Not recommended **Lactation:** Not recommended Specific contraindications have not been determined.

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
	Thrombocytopenia Platelet count 20 - 49 x 10^9/L with baseline platelets ≥100 x 10^9/L: Reduce daily dose by 50 mg from the last given dose; discontinue use in patients unable to tolerate 100 mg OD Platelet <20 x 10^9/L: Interrupt treatment		
Fedratinib	**Myelofibrosis, intermediate-2 or high-risk, primary or secondary** Baseline platelet count >50 x 10^9/L: 400 mg OD PO **Renal impairment** CrCl 15 - 29 mL/min: Reduce dose to 200 mg OD PO **Hepatic impairment** Total bilirubin ≥3x ULN: Avoid use **Hepatoxicity (Grade 3 or higher ALT, AST, or bilirubin elevations):** Interrupt until resolved to Grade 1 or lower or baseline **Nausea, vomiting, or diarrhoea (Grade 3 or higher not responding to supportive measures within 48 hours):** Interrupt until resolved to Grade 1 or lower or baseline **Neutropenia (Grade 4):** Interrupt until resolved to Grade 2 or lower or baseline **Other non-haematologic toxicity (Grade 3 or higher):** Interrupt until resolved to Grade 1 or lower or baseline **Thrombocytopaenia (Grade 3 with active bleeding or Grade 4):** Interrupt until resolved to Grade 2 or lower or baseline **Transfusion-dependent (onset during treatment):** Consider dose reduction	Endocrine metabolic: Thiamine deficiency Gastrointestinal: Diarrhoea, Nausea, Vomiting Haematologic: Anaemia, all grades Neurologic: Asthaenia Other: Fatigue	**Pregnancy**: Not recommended **Lactation**: Not recommended **Boxed Warning** Encephalopathy including Wernicke's

Drug	Recommended Dose, Administration and Adjustment	Common Adverse Effects	Pregnancy and Lactation / Precautions / Remarks
Pacritinib	**Myelofibrosis, intermediate or high-risk, primary or secondary, with platelets <50 x 10^9/L:** 200 mg BD PO **Renal impairment** eGFR <30 mL/min: Avoid use **Hepatic impairment [moderate (Child-Pugh B) or severe (Child-Pugh C)]:** Avoid use **Diarrhoea (Grade 3 or 4):** Withhold until the diarrhoea resolves to Grade 1 **Haemorrhage:** **Bleeding (Grade 2 - 3), intervention indicated:** Withhold until haemorrhage resolves **Life-threatening bleeding, urgent intervention indicated:** Discontinue use **QT interval prolongation (corrected QT prolongation ≥500 msec or ≥60 msec from baseline):** Withhold pacritinib **Thrombocytopenia (clinically significant worsening of thrombocytopenia >7 days):** Withhold pacritinib	Cardiovascular: Peripheral oedema Gastrointestinal: Diarrhoea, Nausea Haematologic: Anaemia, Haemorrhage, Thrombocytopenia Nervous system: Dizziness Respiratory: Epistaxis Other: Fever	**Pregnancy**: Not recommended **Lactation**: Not recommended

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BD = *bis in die*/twice a day; CAPD = continuous ambulatory peritoneal dialysis; CNS = central nervous system; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; CVVHD = continuous veno-venous hemodialysis; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; g/dL = gram per decilitre; Hb = haemoglobin; Hct = haematocrit; HU = hydroxyurea; IFN-alfa = interferon-alfa; JAK = Janus kinase; kg = kilogram; L = litre; LMWH = low molecular weight heparin; mcg = microgram; mcg/week = microgram per week; mg = milligram; mg/day = milligram per day; mg/dose = milligram per dose; mg/kg = milligram per kilogram; mg/kg/day = milligram per kilogram per day; mL/min = millilitre per minute; msec = millisecond; NSAID = nonsteroidal anti-inflammatory drug; OD = *omne in die*/once daily; PO = *per os*/by mouth; QID = *quater in die*/four times a day; SC = subcutaneous; ULN = upper limit of normal; WBC = white blood cell

Table 9: Ruxolitinib specific dose adjusment

Baseline platelet levels / Conditions for dose adjustment	≥200 x 10^9/L	100 - 199 x 10^9/L	50 - 99 x 10^9/L
Indication: Myelofibrosis			
Insufficient response	Definition (meets all criteria): • Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% SVR as measured by CT or MRI, **and** • Platelet >125 x 10^9/L at 4 weeks and never <100 x 10^9/L; **and** • ANC >0.75 x 10^9/L		Definition (meets all criteria): • Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% SVR as measured by CT or MRI; **and** • Platelet count remained ≥40 x 10^9/L **and** has not fallen more than 20% in the prior 4 weeks; **and** • ANC >1 x 10^9/L; **and** • Dosage has not been reduced or interrupted in the prior 4 weeks
	Dose adjustment: • Increase by 5 mg BD, no more frequently than every 2 weeks to a maximum of 25 mg BD. • Discontinue treatment after 6 months if no spleen size reduction or symptom improvement		Dose adjustment: • Increase by 5 mg BD, no more frequently than every 2 weeks to a maximum of 10 mg BD. • Limit treatment to no more than 6 months in patients in whom the benefits outweigh the risks • Discontinue if there is no spleen size reduction or symptom improvement after 6 months
Thrombocytopenia	**When platelet reduced to the following level after initiation:** **Platelet 100 - 125 x 10^9/L** • Consider dose reductions to prevent interruption of therapy as follows:		**When platelet reduced to the following level after initiation:** **Platelet 25 - 35 x 10^9/L and platelet decline is <20% during the prior 4 weeks**

Baseline platelet levels / Conditions for dose adjustment	≥200 x 10^9/L	100 - 199 x 10^9/L	50 - 99 x 10^9/L
	○ 25 mg BD reduce to 20 mg BD ○ 20 mg BD reduce to 15 mg BD ○ no change for 15 mg, 10 mg or 5 mg BD **Platelet 75 - 99 x 10^9/L** ● Consider dose reductions to prevent interruption of therapy as follows ○ 25 mg, 20 mg, or 15 mg BD reduce to 10 mg BD ○ no change for 10 mg or 5 mg BD **Platelet 50 - 74 x 10^9/L** ● Consider dose reductions to prevent interruption of therapy as follows: ○ 25 mg, 20 mg, 15 mg, or 10 mg BD reduce to 5 mg BD ○ no change for 5 mg BD		● Reduce dose as follows: ○ >5 mg OD, reduce by 5mg OD ○ no change for 5 mg OD **Platelet 25 - 35 x 10^9/L and platelet decline is ≥20% during the prior 4 weeks** ● Reduce dose as follows: ○ >5 mg BD, reduce by 5mg BD ○ 5 mg BD reduce to 5 mg OD ○ no change for 5 mg OD
Myelosuppression	**When platelet reduced to the following level after initiation:** **Platelet <50 x 10^9/L or ANC <0.5 x 10^9/L:** ● Interrupt therapy until recovery of platelet >50 x 10^9/L and ANC >0.75 x 10^9/L ● Restart at the higher of 5 mg OD or 5 mg BD below the largest dose in the week prior to dose interruption ● The maximum restarting dose are: ○ 20 mg BD if current platelet ≥125 x 10^9/L ○ 15 mg BD if current platelet 100 - 125 x 10^9/L		**When platelet reduced to the following level after initiation:** **Platelet <25 x 10^9/L or ANC <0.5 x 10^9/L:** ● Interrupt therapy until recovery of platelet >35 x 10^9/L and ANC >0.75 x 10^9/L ● Restart at the higher of 5 mg OD or 5 mg BD below the largest dose prior to dose interruption

<table>
<tr><th>Baseline platelet levels
Conditions for dose adjustment</th><th>≥200 x 10^9/L</th><th>100 - 199 x 10^9/L</th><th>50 - 99 x 10^9/L</th></tr>
<tr><td></td><td colspan="2">○ 10 mg BD if current platelet 75 - 100 x 10^9/L (treat for at least 2 weeks, if stable, may increase to 15 mg BD)
○ 5 mg BD if current platelet 50 - 75 x 10^9/L (treat for at least 2 weeks, if stable, may increase to 10 mg BD)</td><td></td></tr>
<tr><td colspan="4">Indication: Polycythaemia vera</td></tr>
<tr><td rowspan="2">Insufficient response</td><td colspan="3">Definition (meets all criteria):
● one or more; continued need for phlebotomy and/or WBC >ULN and/or platelet >ULN, and/or palpable spleen reduced by <25% from baseline, and
● platelet ≥140 x 10^9/L, and
● Hb ≥12 g/dL, and
● ANC ≥1.5 x 10^9/L</td></tr>
<tr><td colspan="3">Dose adjustment:
● Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.
● Increase by 5 mg BD to a maximum of 25 mg BD if insufficient response and platelet, Hb and neutrophil counts are adequate.</td></tr>
<tr><td>Myelosuppression</td><td colspan="3"><table><tr><th>Blood counts</th><th>Dosage adjustment recommendations</th></tr><tr><td>Hb ≥12 g/dL AND
Platelet ≥100 x 10^9/L</td><td>No adjustment required</td></tr></table></td></tr>
</table>

Baseline platelet levels / Conditions for dose adjustment	≥200 x 10^9/L	100 - 199 x 10^9/L	50 - 99 x 10^9/L
	Hb 10 - 12 g/dL AND Platelet 75 - 100 x 10^9/L: Consider dosage reduction with the goal of avoiding dose interruptions for anaemia and thrombocytopenia Hb 8 - 10 g/dL OR Platelet 50 - 75 x 10^9/L: Reduce dosage by 5 mg BD, or 5 mg BD reduce to 5 mg OD Hb <8 g/dL OR Platelet <50 x 10^9/L OR ANC <1 x 10^9/L: Interrupt therapy. Restart with a dose no more than 5 mg BD lesser than the dosage which resulted in interruption. Use most severe abnormal value to determine maximum restarting dosage: • For recovery of Hb 8 - 10 g/dL or platelet 50 - 75 x 10^9/L or ANC 1 - 1.5 x 10^9/L, restart at maximum 5 mg BD for at least 2 weeks, and if stable, may increase dosage by 5 mg BD. • For recovery of Hb 10.1 - 12 g/dL or platelet 76 - 100 x 10^9/L or ANC 1.6 - 2 x 10^9/L, restart at maximum 10 mg BD for at least 2 weeks, and if stable may increase dosage by 5 mg BD. • For recovery of Hb >12 g/dL or platelet >100 x 10^9/L or ANC >2 x 10^9/L, restart at maximum 15 mg BD for at least 2 weeks, and if stable, may increase by 5 mg BD. • Patients who had required dose interruption while receiving a dose of 5 mg BD, may restart at a dose of 5 mg OD, but not higher, once Hb ≥10 g/dL, platelet ≥75 x 10^9/L and ANC ≥1.5 x 10^9/L. • Dose management after restarting treatment, after restarting ruxolitinib following treatment interruptions, doses may be titrated, but the maximum total daily dose should not exceed 5 mg lesser than the dose that resulted in the dose interruptions. An exception to this is dose interruption following phlebotomy-associated anaemia, in which case the maximal total daily dose allowed after restarting ruxolitinib would not be limited.		

Abbreviations: ANC = absolute neutrophil count; BD = *bis in die*/twice a day; CT = computed tomography; g/dL = gram per decilitre; Hb = haemoglobin; L = litre; MRI = magnetic resonance imaging; mg = milligram; OD = *omne in die*/once daily; SVR = spleen volume reduction; ULN = upper limit of normal; WBC = white blood cell

Source:
1. Tatarsky I, Sharon R. Management of polycythemia vera with hydroxyurea. Semin Hematol. 1997;34(1):24-28.
2. Löfvenberg E, Wahlin A. Management of polycythaemia vera, essential thrombocythaemia and myelofibrosis with hydroxyurea. Eur J Haematol. 1988;41(4):375-381.
3. U.S. Food and Drug Administration. Product Information: HYDREA(R) oral capsules, hydroxyurea oral capsules. USFDA; 2016.
4. Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol. 2019;20(4):e200-e207.
5. U.S. Food and Drug Administration. Product Information: SIKLOS(R) oral tablets, hydroxyurea oral tablets. USFDA; 2023.
6. U.S. Food and Drug Administration. Product Information: DROXIA(R) oral capsules, hydroxyurea oral capsules. USFDA, 2023.
7. U.S. Food and Drug Administration. Product Information: AGRYLIN(R) oral capsules, anagrelide HCl oral capsules. USFDA; 2018.
8. U.S. Food and Drug Administration. Product Information: DURLAZA(TM) oral extended release capsules, aspirin oral extended release capsules. USFDA; 2015.
9. U.S. Food & Drug Administration. FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid. (accessed online on 9 May 2025). USFDA; 2022. [Available at: https://www.fda.gov/media/142967/download]

LIST OF ABBREVIATIONS

AE	adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation
aGVHD	acute graft-vs-host disease
allo-HCT	allogenic hematopoietic stem cell transplant
AML	acute myeloid leukaemia
AMM	Academy of Medicine of Malaysia
ASTCT	American Society for Transplantation and Cellular Therapy
ATE	arterial thromboembolism
BAT	best available therapy
BD	*bis in die*/twice a day
BFI	Brief Fatigue Inventory
BM	bone marrow
BSH	British Society for Haematology
C&G	Campbell and Green
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
cm	centimetre
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukaemia
CMV	cytomegalovirus
COMFORT	Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment
CPG	clinical practice guidelines
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
cGVHD	chronic graft-vs-host disease
CYTO-PV	Cytoreductive Therapy in Polycythemia Vera
DFS	disease-free survival
DG	Development Group
DIPSS	Dynamic International Prognostic Scoring System
DIPSS+	Dynamic International Prognostic Scoring System-Plus
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulants
DVT	deep vein thrombosis
e.g.	*exempli gratia*/for example
EBMT	European Society for Blood and Marrow Transplantation
EFS	event-free survival
EPO	erythropoeitin
ES	effect size
ESMO	European Society for Medical Oncology
ESR	erythrocyte sedimentation rate
ET	essential thrombocythaemia
etc.	*et cetera*/and other similar things
ELN	European Leukaemia Net
FBC	full blood count
FBP	full blood picture
FMS	family medicine specialist
g/day	gram per day
g/dL	gram per decilitre
GHS	Global Health Status

GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and valuation
Hb	haemoglobin
Hct	haematocrit
HES	hypereosinophilic syndrome
HMR	high molecular risk
HR	hazard ratio
HTA	health technology assessment
HU	hydroxyurea
i.e.	*id est*/that is
ICSG	Italian Cooperative Study Group
IFN	interferon
IFN-α	interferon alpha
IPSET	International Prognostic Score for Thrombosis in Essential Thrombocythaemia
IPSET-t	International Prognostic Score for Thrombosis in Essential Thrombocythaemia-thrombosis
IPSS	International Prognostic Scoring System
ITT	intention-to-treat
IV	intravenous
JAK	Janus kinase
JAK-STAT	Janus kinase/signal transducers and activators of transcription
L	litre
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
MaHTAS	Malaysian Health Technology Assessment Section
MCV	mean corpuscular volume
MEDAS	Mediterranean Diet Adherence Screener
MF	myelofibrosis
µg/dL	microgram per decilitre
MI	myocardial infarction
mm	millimetre
MoH	Ministry of Health
MPD-RC	Myeloproliferative Disorders Research Consortium
MPN(s)	myeloproliferative neoplasm(s)
MPN-SAF	Myeloproliferative Neoplasm - Symptom Assessment Form
MPN-SAF	Myeloproliferative Neoplasm - Symptom Assessment Form
TSS	Total Symptoms Score
MPN-U	unclassifiable myeloproliferative neoplasm
MSD	matched sibling donor
MUD	matched unrelated donor
MYSEC-PM	Myelofibrosis Secondary to PV and ET Prognostic Model
NCCN	National Comprehensive Cancer Network
NGS	next generation sequencing
NRM	non-relapse mortality
NS	not significant
OD	*omnie die*/once a day
OR	odds ratio
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PE	pulmonary embolism

PEG-IFN	pegylated interferon
PMF	primary myelofibrosis
PV	polycythaemia vera
QoL	quality of life
r-IPSET-t	International Prognostic Score for Thrombosis in Essential Thrombocythaemia-thrombosis
RBC	red blood cell
RCT	randomised controlled trial
RR	relative risk/risk ratio
SAC	sensitivity analysis cohort
SCC	stringent criteria cohort
SEER	Surveillance, Epidemiology and End Results
SGLT2	sodium-glucose co-transporter 2
SIMPLIFY	Momelotinib versus Ruxolitinib in Subjects with Myelofibrosis
SRR	spleen response rate
SVR	spleen volume reduction
TRM	transplant-related mortality
TSS	total symptoms score
TTR	time in therapeutic range
U.S.	United States
U/L	units per litre
USDA	U.S. Dietary Guideline for Americans
USG	ultrasonography
USPSTF	United States Preventive Services Task Force
VAF	variant allele frequency
VAS	Visual Analogue Scale
VHR	very high risk
VKA	vitamin K antagonist
VTE	venous thromboembolism
WBC	white blood cell
WHO	World Health Organization

ACKNOWLEDGEMENT

The members of CPG DG would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft technically
- Technical Advisory Committee of CPG for their valuable input and feedback
- HTA and CPG Council for approval of the CPG
- Dato' Dr. Goh Ai Sim and Datuk Dr. Noel Thomas Ross for their involvement and feedback on the protocol of the CPG
- Mr. Latif Abqari Nazeri for the retrieval of evidence
- Dr. Ahmad Shamil Semanat for the cover of the CPG
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both DG and RC had completed disclosure forms. None hold shares in pharmaceutical firms or act as consultants to such firms. Details are available upon request from the CPG Secretariat.

SOURCE OF FUNDING

The development of the CPG on Management of Myeloproliferative Neoplasms (Second Edition) was supported financially in its entirety by the MoH.

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
62590 Putrajaya, Malaysia

eISBN 978-629-7842-19-6